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1894. Evans, W. Arnold, M.D., Town Hall, Bradford.
1897. Fraser, A. M., M.D., Town Hall Portsmouth.
1903. Freeman, E. C., M.R.C.S., L.R.C.P., Major R.A.M.C., care of Holt and Co., 3, Whitehall Place, S.W.
1904. Grünbaum, A. S. F., M.D., F.R.C.P., 38, Clarendon Road, Leeds.
1903. Hendley, A. G., Major, I.M.S., c/o Grindlay & Co., Bombay.
1892. Horne, T., M.D., Town Hall, Stockton on-Tees.
1889. James, A. W., 69, Gloucester Terrace, Hyde Park, W.
1902. Lewis, C. J., M.D., D.Sc. 13, Walker Street, Edinburgh.
1899. Low, J. Spencer, M.B., Helmsley House, Christchurch Road, Tulse Hill.
1897. Lowson, J. A., care of Mrs. Grant, Craiglachie, Keswick Road, Putney, S.W.
1872. Moore, Sir J. W., M.D., 40, Fitzwilliam Square West, Dublin.
1894. Pattin, H Cooper, M.D., Municipal Offices, Norwich.
1875. Ransome, Arthur, M.D., F.R.S., Sunnyhurst, Dean Park, Bournemouth.
1898. Rogers, Leonard, M.D., F.R.C.S., I.M.S. Major; care of Thos. Cook and Son, 9, Old Court House, Calcutta.
1894. Weston, G. H., M.D., Shirley, Southampton.
1898. Williams, H. J. E. H., M.D., City Hospital, Winter Street, Sheffield.
1888. Wilson, J. Mitchell, M.D., County Hall, Beverley, Yorks.

Non-Resident Members.

1896 Adams, P. T., M.D., Bloemfontein, O.R.C.
1903. Armstrong, W. G., M.B., Department of Public Health, City Town Hall, Sydney, N.S.W.
1894. Atkinson, M., M.D., Hong Kong.
1888. Bately, J., M.D., High Street, Gorleston, Great Yarmouth.

Elected

1895. Borthwick, T., M.D., Kensington, Adelaide, South Australia.
1883. Bovill, Surg. Lieut.-Col. Edward, M.D., C.M., I.M.S., Bengal, India (*retired*).
1889. Bruce, David, M.B., Lieut.-Col. R.A.M.C., c/o War Office.
1864. Buckle, Fleetwood, M.D., 20, Merton Road, Southsea (*retired*).
1904. Bushnell, F. G., M.D., D.P.H., Sussex County Hospital, Brighton.
1887. Collins, G. W., The Mall, Wanstead, N.E.
1885. Corney, Bolton G., Suva, Fiji; and 26, Bedford Place, Russell Square, W.C.
1885. Crawford, D. G., Lieut-Col. I.M.S., Mymensingh, Lower Bengal.
1902. Crawford, G. S., D.P.H., Major R.A.M.C., Ashford Cargate, Aldershot.
1891. Crook, H. E., M.D., 23, Dalby Square, Cliftonville, Margate.
1876. Day, E. J., Dorchester.
1886. Donovan, Justin F., M.D., Port Royal, Jamaica.
1898. Eaton, Oliver, Westcott, Exmouth.
1888. Fosbroke, G. H., M.D., Shire Hall, Worcester.
1890. Garrett, J. H., M.D., Municipal Offices, Cheltenham.
1876. Hardwicke, H. Junius, M.D., 13, Magdalen Terrace, St. Leonard's-on-Sea.
1880. Harrison, R. Charlton, M.D., 19, Uxbridge Road, Ealing, W.
1881. Henderson, G. C., M.D., Kingston, Jamaica.
1882. Herring, John F., St. Mary's House, Atherstone, Warwickshire.
1875. Hime, T. W., M.D., 54, Horton Road, Bradford.
1881. Irwin, Chauncey Graves, M.D. (*retired*), Dep.-Surg.-Gen., Casa Hatfield, St. Albans, Herts.
1886. Lingard, A., M.B., Imperial Bacteriologist, Muktesar, Kumâon Hills, N.W.P., India.
1860. May, George, M.B., F.R.C.S. (*retired*), The Warren, Caversham. Reading.
1899. Millard, C. K., M.D., B.Sc., Town Hall, Leicester.
1890. M'Neill, R., M.D., Argyll County Council, Oban, N.B.
1900. Moffet, G. E., Surg.-Major, R.A.M C., 5, Castle Street, Brechin, Forfarshire.
1897. Pakes, W. C., M.D., Government Laboratory, Pretoria, South Africa.
1874. Reid, Walter, M.D., Dep. Inspector-General, Royal Naval Hospital, Haslar (*retired*).
1863. Rowe, T. Smith, M.D., 1, Union Crescent, Margate.
1881. Russell, E. G., M.B., B.Sc., Surg. Lieut.-Col., I.M.S. Bengal Army (*retired*).
1884. Simpson, W.J., Professor, M.D., King's College.
1899. Snell. E. H., M.D., 80, Hay Lane, Coventry.
1903. Stokes, E. S., M.B., Department of Public Health, Sydney, N.S.W.
1889. Street, A. F., M.D., St. Mildred's Road, Westgate-on-Sea, Kent.
1885. Sturridge, P. F., Stramongate, Kendal, Westmorland.
1876. Turner, G., M.D., Cape Town, South Africa.
1888. Walford, Edward, M.D., Municipal Offices, Cardiff.
1893. Whiston, P. H., Surgeon-Major, R.A.M.C., Junior United Service Club, S.W.; Charles Street, St. James', S.W.
1884. Williamson, R. E., M.B., Romagna House, Otley, Yorks.

Corresponding Members.

Elected

1894. Catrin, L., Dr., Val-de-Grâce, Paris.
1856. Cox, Wm. Isidore, Hawkesbury-Upton, Chippenham, Gloucestershire.
1871. Cuningham, J. M., M.D., C.S.I., Surg.-Gen. Ind. Med. Dept., Sanitary Commissioner of Govt. of India (*retired*).
1894. Davidson, T. R., M.D., 30, Morningside Place, Edinburgh.
1878. Delmas, Louis H., M.D., P.O. Box 524, Havana, Cuba.
1895. Gache, Samuel, M.D., Buenos Ayres, Argentine Republic.
1892. Hauser, Philip, M.D., Madrid.
1889. Hewitt, Chas. N., M.D., Red Wing, Minnesota, U.S.A.
1900. Holst, Axel, M.D., Professor of Hygiene in the University of Christiania, Norway.
1857. Leaõ, Jose Fernandes da Silva, Cape de Verde.
1900. Linroth, Klas, M.D., Medical Officer of Health of Sweden, Stockholm.
1900. Mosny, Ernest, M.D., Médecin des Hôpitaux de Paris, Comité Consultatif d'Hygiene Publique de France.
1894. Netter, Dr. Arnould, 129, Boulevard St. Germain, Paris.
1854. Purple, S. S., M.D., New York, U.S.A.
1886. Rochard, G., M.D., Paris.
1900. Schierbeck, Niels Peter, M.D., Chief of the Hygiene Laboratory, University of Copenhagen, Denmark.
1888. Thompson, Ashburton, M.D., 93, Macquarie Street, Sydney, New South Wales.
1905. Vincent, Professor H., École du Val de Grâce, 277bis, Rue St. Jacques, Paris.
1861. Whitelaw, Wm., M.D., Kirkintilloch, Dumbartonshire.

Jenner Medallists.

1898. William Henry Power, C.B., F.R.S., Chief Medical Officer of the Local Government Board, Whitehall, S.W.
1902. A. Laveran, Membre de l'Institut et de l'Academie de Medicine, 25, Rue du Montparnasse, Paris.

TRANSACTIONS

OF

The Epidemiological Society of London.

INAUGURAL ADDRESS OF SESSION 1906–1907.

On Tuberculosis.

By JOHN TATHAM, M.A., M.D., F.R.C.P.,
President of the Society.

(*Delivered: November* 16*th*, 1906.)

I HAVE availed myself of the opportunity afforded me by the custom of our Society respecting an Address from the Chair, to review, with the help of the most recent available information, the behaviour of fatal tuberculosis in England and Wales, throughout the period that has elapsed since the establishment of civil registration. I am, of course, aware—indeed, it is familiar knowledge to all of us—that rates of mortality from this, as well as from other prevalent diseases, have been published year after year in the reports of the Registrar-General, and that these rates have been frequently quoted by writers on medical statistics. How, then, can one justify the republication of data which have long been common property? No one can be more fully conscious than I am of the danger of drawing false conclusions from statistics which, as in the present case, depend on variable factors, and on evidence which, in respect of the earlier years at any rate, can scarcely be accepted as absolutely reliable.

I have been engaged for a considerable portion of my leisure time since the last Census in studying the incidence of disease in England and Wales, with the help of the data concerning population and occupation then obtained. Amongst other diseases, I have specially considered the question of fatal tuberculosis; and my object on the present occasion is to place before you some interesting facts and considerations relative to the loss of life still caused in England by this terrible scourge, and to compare the present loss of life with that obtaining in the earlier

years of the last half century. My reason for asking your attention at the present time to the distribution of fatal tuberculosis is this—that the rates which I now submit, and which form the basis of the accompanying tables, differ materially from those with which you are already familiar; especially is this the case with respect to the earlier years of the series.

These latter rates, although originally calculated with great care, are based on the shifting age and sex constitution of the English population, as ascertained at the respective Census enumerations. If the death-rates of past years had been calculated throughout on a population of uniform constitution with respect to age and sex, they would, of course, have been fairly comparable, and the very considerable labour that has been expended on their re-calculation would have been unnecessary. Unfortunately, however, this is not the case. On the contrary, in the course of the last half century, the population of this country has changed so considerably as to seriously impair the comparability of the earlier data with those of more recent years.

Accordingly, in order to secure a better basis of comparison, I have applied the deaths registered in the several years from 1851 onwards to a standard population of uniform constitution in these respects, the standard adopted being that of the enumerated population of England and Wales at the Census of 1901. Whether or not the labour devoted to this task is justified by the results I leave you to judge. For myself, I confess that in their revised form I have greater confidence in comparing the rates of the present with those of the past than I should have had in the absence of such revision,

In attempting to trace through a long series of years the changes of mortality from a widespread and terribly-destructive malady like tuberculosis, certain precautions must be observed.

At the outset, it is necessary to bear in mind that the causes of death were not abstracted in combination with the ages at death until the year 1847.

It will be remembered that the Birth and Death Registration Act, which imposed upon medical men the duty of formally certifying the cause of death of their patients dates only from the year 1874. Nevertheless, for many years previously, in fact, ever since the issue of the remarkable appeal, which, in 1837, the Presidents of the Royal Colleges of Physicians and Surgeons and the Master of the

Society of Apothecaries addressed to practitioners, the cause of death of their patients had been, for the most part, loyally attested, for national registration purposes, by medical men. Still, it cannot, of course, be contended that purely voluntary returns of this kind are equally satisfactory with the statutory returns which are now made to Somerset House under the Statute of 1874.

Again, in the earlier years of the last half century, it was the practice, in remote parts of England and Wales, to regard as phthisical all respiratory complaints attended with expectoration or with wasting. Moreover, in some parts of the country, about one-seventh part of the total deaths were at one time uncertified, the patients having been attended—if at all—by irregular practitioners.

Having regard to the foregoing considerations, it is probable that the mortality by tuberculosis in the early part of the last half century was, through no one's fault, represented in the returns with less accuracy than is desirable for statistical purposes.

It has frequently been contended, by myself and by others, that a serious difficulty besets our attempts to determine for a given time or place the amount of mischief actually caused by tuberculosis, by reason of uncertainty as to the true nature of the morbid conditions denoted by certain time-honoured names used in medical certificates, presumably to indicate tuberculous disease. In the diagnosis of pulmonary tuberculosis, at any rate in its later stages, there is little danger of serious error, but the identification of some other forms of tuberculosis is attended with greater difficulty.

To tuberculous disease, in one or another form, one-ninth part of the deaths from all causes were ascribed in the decade 1891-1900.

Elsewhere I have shown that the total mortality from tuberculous disease has fallen by fully one-third part within the last half century, in the course of which period considerable changes have taken place in the fatality of its several forms. For whilst, on the one hand, tuberculosis of the lung, the brain, and the peritoneum, has decreased considerably in fatality, on the other hand, there has been an increase in the fatality of some other manifestations of tuberculosis—*e.g.*, from tuberculous affections of the bones and other organs not previously mentioned.

In the ten years, 1891-1900, out of every hundred deaths from tuberculous disease, 69 were ascribed to phthisis, 11 each to tuberculous meningitis and tuberculous peri-

tonitis (with tabes mesenterica), and nine to other forms of tuberculosis. It will be interesting to inquire whether the above-named proportions, contributed by the various forms of tuberculous disease, are approximately correct. The following considerations may be serviceable in this connection :—

1. As is the case with many other diseases, the system of periodical inquiry, initiated in 1880, has considerably altered the apparent incidence of mortality from all forms of tuberculosis. It is an unfortunate and unlooked-for result of our recent endeavours to improve medical nomenclature, that some very able and conscientious practitioners frequently omit to state the organ affected by tuberculosis, the consequence being that many deaths from tuberculous phthisis are now returned as from "tuberculosis" simply; and therefore the deaths appearing in the registers under "phthisis" or "pulmonary tuberculosis" are fewer than they should be, whilst those returned as from "tuberculosis," are correspondingly in excess. This practice has obtained only in recent years, so that its effect on the relative incidence of at least two forms of tuberculous disease is very appreciable. In this connection it is a significant fact that in the decennium ended 1890, the proportion of tuberculous mortality contributed by phthisis was higher by about two per cent. than in the decennium recently ended.

2. With respect to the mortality under the head of tuberculous meningitis, it is to be remarked that even at the present time about 6000 deaths are returned annually in this country as from simple "meningitis," although the mortality thus returned is decreasing rapidly. Now I think I shall be correct in stating that meningitis unconnected with parasitic invasion is a rare condition; and I cannot help thinking that if autopsies on the bodies of children dying of brain affections were the rule instead of the exception, as they are at present, a considerable portion of these 6000 deaths would be attributed to tuberculous invasion. On the other hand, it is certain that some of the deaths now referred to this cause would, in the event of post-mortem examination, be referred to other kinds of infection.

3. How many of the deaths from tabes mesenterica are really tuberculous? I do not pretend to answer this question, but I know that, in consequence of the difficulty of obtaining autopsies, many hospital physicians very

properly hesitate to certify deaths from abdominal diseases of this sort, as being due to tuberculosis.

As regards the large number of deaths occurring annually in the homes of the poor, it is scarcely to be wondered at that mistakes should sometimes be made: either by erroneously referring non-tuberculous deaths to tabes mesenterica, or by attributing to marasmus some deaths which are really due to tuberculous affections of the mesentery or of the intestines.

I am thankful to say, however, that the objectionable term tabes mesenterica is now rapidly falling into disuse. It has been suggested to me, by hospital physicians and surgeons of repute, that in many instances more accurate registration of death causes would result if means were available by which a diagnosis often hurriedly arrived at for registration purposes could be afterwards revised. For example, in cases where autopsies have been secured subsequently to the granting of the statutory death-certificate, it is suggested that correction of the certificate is desirable in the interests of scientific medicine. Fully in sympathy myself with this suggestion, I desire to make it known that in any case where a medical practitioner desires to modify in this way a certificate previously given, he has only to communicate his wish to the Statistical Department of the Registrar-General's Office, and we shall gratefully make the requisite correction in the Tables of *Vital Statistics;* although, as you are probably aware, the actual registers cannot be altered except by statutory process.

Phthisis.—Of all the forms of tuberculous disease, phthisis is, as has already been stated, by far the most fatal; the death-rate in the decennium last ended having averaged 1391 per million living at all ages, and of both sexes, as against an average of 2730 per million in the decennium 1851-60. The death-rate from phthisis has therefore fallen by 49 per cent within the last fifty years.

Since the year 1851, phthisis fatality has varied remarkably, with respect both to sex and to age. The Table on the next page shows that in the decennium 1851-60 phthisis was more fatal to females than to males, whilst in the decennium just ended the reverse was the case. The Table further shows that among children under five years phthisis mortality in the decennium 1891-1900 was 441 per million in boys and 385 in girls; in the next quinquennium of age the rates were 174 and 239 respectively. In both sexes it is with the approach of puberty that the real liability to

death by phthisis begins, and this is true of recent as well as of earlier years.

Taking the decennium ended 1900, it will be seen that at the age-group 15-20 years, males succumbed to phthisis in the proportion of 995 and females in the proportion of 1290 per million living, of each sex. From this age the mortality increases steadily as one decade succeeds another, attaining the maximum at the age 45-55 in men, and ten years earlier, viz., 35-45, in women, at which ages respectively the rates are 3144 and 2121 per million. The mortality thereafter declines, at first slowly, and then more rapidly until the close of life. From this Table it appears

Phthisis.—Death-Rates per Million living in the Decennia 1851-60 and 1891-1900.

Age-Groups.	Both Sexes.			Males.			Females.		
	1851-60.	1891-1900.	Ratio.[1]	1851-60.	1891-1900.	Ratio.[1]	1851-60.	1891-1900.	Ratio.[1]
All ages ...	2730[2]	1391	51	2625[2]	1580	60	2828[2]	1214	43
0 –	1310	413	32	1333	441	33	1287	385	30
5 –	573	206	36	526	174	33	621	239	38
10 –	1027	368	36	764	234	31	1294	502	39
15 –	2964	1144	39	2398	995	42	3523	1290	37
20 –	4184	1730	41	4054	1887	46	4302	1591	37
25 –	4319	2135	49	4029	2369	59	4583	1923	42
35 –	4109	2592	63	4016	3095	77	4197	2121	51
45—	3479	2362	68	3840	3144	82	3134	1642	52
55 –	2852	1881	66	3346	2618	78	2394	1239	52
65 –	1989	1154	58	2394	1584	66	1640	807	49
75 and up.	808	437	54	927	556	60	717	352	49

[1] *i.e.*, the ratio of the mortality in 1891-1900 to that of 1851-60, the latter taken as 100.

[2] Based on the age-constitution of the mean population of England and Wales in 1891-1900.

that females are *less liable* than males to die of phthisis at ages under five years, *more liable* at ages from five to twenty years, and again *less liable* at subsequent ages.

The foregoing Table indicates that since 1851-60 phthisis mortality among males at all ages has been reduced by about two-fifths, having fallen among males from a rate of 2625 to a rate of 1580 per million living; and that among females it has been reduced by more than half, having fallen from 2828 to 1214 per million. The Table clearly shows that, although in varying degrees, the improvement which these rates express has been shared by

persons of both sexes and at every age-group. Generally speaking, the amount of reduction is greatest among the young, and least among the middle-aged. Taking separately the figures relating to each sex, it will be seen that among males up to the age of 25 the mortality has been reduced by more than 50 per cent. From that year of age until the age-group 45-55, the amount of improvement gradually diminishes, but at subsequent ages increases again. Among females the amount of reduction is spread more uniformly over the various ages, being equal to nearly 60 per cent. up to the 25th year, and to nearly 50 per cent. thereafter. It is worthy of note that among young children the mortality ascribed, in the later decennium, to this form of tuberculous disease is only one-third of that so ascribed in the earlier decennium.

Careful examination of the records suggests the probability that the reduction indicated by the Table, although in great part real, is not wholly so. It has already been stated that in the 'fifties and 'sixties of last century a considerable portion of the deaths were uncertified. In those days many persons died without medical attention; and even in cases where medical aid had been received in the last illness, there was no legal requirement that the cause of death should be certified. Moreover, in remote parts of the country many fatal cases of lung affection associated with expectoration were put down without question as phthisical.

The following Table shows the local distribution of fatal phthisis in two selected areas, representing urban and rural England respectively. The figures indicate (1) crude and (2) corrected rates of mortality at all ages, per million living of each sex, in the ten years 1891-1900.

—	Crude Rates.		Corrected Rates.	
	Urban County Group.	Rural County Group.	Urban County Group.	Rural County Group.
Males	1770	1307	1753	1347
Females ...	1263	1199	1250	1240
Both sexes ...	1508	1251	1493	1292

From this Table we learn that in both areas phthisis is more fatal to males than to females, but that the excess is by far the greatest in the urban county group: the male rate exceeding the female by not more than nine per cent. in the rural area, whilst the corresponding excess in the urban area amounts to 40 per cent.

The next Table shows the distribution of phthisis mortality, by registration counties, in two decennial periods separated by an interval of ten years.[1]

Disregarding counties with populations of fewer than 100,000 persons, the areas with the lowest uncorrected death-rates from phthisis in the decennium ended 1900 were the counties of Buckingham, Worcester, Monmouth, Wilts, and Middlesex. The counties with the highest rates were London, where the rate was 1790 per million; Northumberland, 1717; Lancashire, 1583; and Hants, 1505.[2]

If the rates in the decennium 1881-90 be compared with those of the decennium last ended, it will be seen that the counties which had been amongst the greatest sufferers from phthisis in the earlier period were also those in which the mortality was highest in the later period. In the absence of the necessary returns, it has not been practicable to trace the influence of season on phthisis mortality for England and Wales generally. In London, however, in the five years 1901-5, 27.3 per cent. of the mortality from phthisis occurred in the first quarter of the year, and 27.1 per cent. in the fourth quarter; whilst 23.7 and 21.9 per cent respectively occurred in the second and third quarters of the year.

Tuberculous Meningitis.—In the decennium ended 1900, the general mortality from tuberculous meningitis, including acute hydrocephalus, was lower than that of the preceding decennium by eight per cent.

Inasmuch as about 72 per cent. of the total deaths from this affection occur in children under five years old, it will be convenient to deal here with the distribution of mortality at that stage of life. Among young children, the mortality

[1] The rates in this Table are corrected for age- and sex-differences of population.

[2] The phthisis-mortality in Hampshire is unfairly increased by the presence, in the Isle of Wight and in the neighbourhood of Bournemouth, of several hospitals for the treatment of that disease. In the year 1904, there occurred in Consumption Hospitals within the county 50 deaths, of which 47 were those of non-residents. If these deaths are deducted, the Hampshire phthisis death-rate of males will be reduced from 1720 to 1627 per million, and that of females will be reduced from 1863 to 1038.—*Sixty-Seventh Annual Report of the Registrar-General*, p. lxxiv.

Phthisis, 1881 *to* 1890, 1891 *to* 1900.

Mean Annual Death-Rates in Registration Counties, corrected for Age- and Sex-Distribution of the Several Populations.

Registration Counties.	Annual Deaths in a Standard Million.						Mortality of Males to that of Females taken as 100 (1891–1900).
	Both Sexes.		Males.		Females.		
	1881-1890.	1891-1900.	1881-1890.	1891-1900.	1881-1890.	1891-1900.	
England and Wales ..	1775	1391	1904	1580	1655	1214	130
London	2058	1738	2520	2208	1624	1297	170
Northumberland ..	2142	1717	2165	1868	2120	1576	119
North Wales	2166	1670	2068	1694	2258	1647	103
Lancashire	1972	1564	2130	1804	1824	1339	135
South Wales	2079	1537	1979	1471	2173	1599	92
Hampshire	1901	1500	2157	1783	1661	1235	144
Durham	1784	1462	1647	1456	1913	1467	99
Warwickshire	1663	1421	1967	1795	1378	1070	168
Devonshire	1760	1391	1826	1562	1698	1287	117
West Riding	1877	1389	2014	1576	1748	1213	130
Suffolk	1849	1352	1810	1415	1886	1293	109
Sussex	1714	1343	1940	1601	1502	1101	145
Cambridgeshire ..	1780	1341	1775	1467	1785	1223	120
Cornwall	1824	1337	1938	1520	1717	1165	130
Cumberland	1698	1313	1653	1310	1741	1318	99
East Riding	1696	1308	1715	1423	1678	1209	119
Cheshire	1640	1286	1711	1401	1574	1179	119
Gloucestershire	1549	1285	1636	1459	1467	1122	130
Kent	1565	1260	1609	1401	1523	1128	124
Hertfordshire	1542	1259	1675	1471	1417	1060	139
North Riding	1541	1218	1430	1213	1646	1223	99
Northamptonshire ..	1482	1206	1500	1320	1465	1099	120
Huntingdonshire ..	1686	1206	1578	1283	1787	1134	113
Surrey	1597	1185	1865	1413	1345	971	146
Norfolk	1590	1183	1549	1194	1628	1173	102
Bedfordshire	1585	1167	1498	1256	1667	1083	116
Lincolnshire	1571	1162	1392	1107	1739	1213	91
Berkshire	1532	1160	1659	1339	1413	992	135
Essex	1516	1156	1564	1289	1471	1031	125
Nottinghamshire ..	1665	1153	1661	1219	1669	1091	112
Derbyshire	1472	1141	1417	1194	1523	1091	109
Somersetshire	1452	1133	1558	1244	1353	1029	121
Staffordshire	1428	1133	1492	1279	1368	996	128
Dorsetshire	1463	1126	1413	1101	1510	1449	96
Shropshire	1462	1122	1440	1184	1483	1064	111
Leicestershire	1351	1121	1436	1266	1271	985	129
Oxfordshire	1469	1110	1554	1256	1390	973	129
Herefordshire	1340	1110	1277	1157	1399	1066	109
Middlesex	1429	1087	1640	1299	1231	888	146
Wiltshire	1562	1085	1525	1159	1597	1016	114
Monmouthshire ..	1488	1047	1310	987	1655	1103	89
Buckinghamshire ..	1379	1045	1330	1099	1425	994	111
Worcestershire	1249	1021	1407	1194	1101	859	139
Westmorland	1451	958	1384	987	1514	930	106
Rutlandshire	1388	925	1279	961	1490	892	108

from tuberculous meningitis increases from birth to the end of the first year, after which age it steadily declines.

In the recent decennium, boys died at the rate of 1481 per million living at the age of 0-5 years, a rate which exceeds that of girls by 320 per million. In the course of the last 40 years, the mortality among boys has decreased by 43 per cent. against a decrease of 37 per cent. among girls.

In the decennium 1891-1900, the mortality from tuberculous meningitis was not separately tabulated for particular areas; but from the data prepared by me for the information of the Committee on Physical Deterioration, it appears that in the quinquennial period ended 1902, this disease was very considerably more fatal to young children in the town than in the country. The actual figures are given at foot.[1]

Tuberculous Peritonitis.—In the decennium last ended, the mortality at all ages referred to tuberculous peritonitis, or to tabes mesenterica, was lower by 16 per cent. than that of the preceding decennium. Of the total deaths, 80 per cent. were those of children under the age of five years, for which reason the following remarks apply almost entirely to the earlier stages of life. The mortality from tuberculous peritonitis is higher in the earlier months of infancy than is that from tuberculous meningitis; but as regards age distribution it somewhat resembles that disease, the mortality rising steadily from birth up to the end of the first year of life, and thereafter gradually declining.

In 1891-1900, the mortality from this disease among boys under five years was equal to 1613 per million living, and among girls of the same age to 1304 per million; the former rates having declined within the last forty years by 19 per cent. and the latter by 24 per cent.

Other Tuberculous Diseases.—Under this heading are included general tuberculosis, scrofula, lupus, and tuberculous affections of the bones, joints, and other parts of the body not specified in the Tables. In the aggregate, the deaths attributed to these causes account for an average mortality of 186 per million of the population.

As in the case of the forms of this infection already dealt with, these diseases are more fatal to males than to females, nearly half the victims being less than five years old. The mortality differs from that of the other specified forms

[1] 1899 to 1902. Deaths of Infants under One Year per 1000 Births:—

	Urban County Group.	Rural County Group.
Tuberculous meningitis	1.98	1.24
Tuberculous peritonitis	3.53	2.07

of tuberculosis, in that it has not fallen in the course of the last forty years. From the Registrar-General's Annual Reports it may be seen that an increase since 1900 has occurred under the head of Tuberculosis of the bones, joints, etc., but that the deaths from "General Tuberculosis" as well as from "Lupus" and from "Scrofula" have shown no increase since that date.

We now come to consider phthisis in relation to the occupations of the people, and in order to facilitate this study, a conventional term—"comparative mortality figure"—has been employed. The total deaths of males at ages from 25-65, which is held to be the main working period of life, being taken at 1000, the figures for individual diseases are expressed by numbers proportional to this figure. These figures are provisional merely, and are subject to revision when the second part of the decennial supplement comes to be published. Among the principal diseases that are tabulated in the national mortality returns, the most destructive at the present time is phthisis: which disease is responsible for 186 out of the deaths from all causes making up the comparative mortality figure of 1000.

In a Table to be published in the forthcoming supplement, the comparative phthisis mortality returns are stated for occupied males of several classes: (*a*) in England and Wales as a whole; (*b*) in London; (*c*) in industrial districts; (*d*) in agricultural districts; and (*e*) for unoccupied males. Among occupied males generally, the comparative mortality figure in the triennial period 1900-01-02 was 175, which is less by 39 than the figure for the corresponding period of the previous decennium.

In London, phthisis gave a comparative mortality figure of 262 in the more recent period, or 59 less than in the earlier. In the industrial districts the figure was 205 in the recent period, or 53 less than in the earlier; and in the agricultural districts the figures were 125 and 157 respectively. When these mortality figures are contrasted with those for unoccupied males, we find that in the triennial period 1900-02, the comparative mortality figure for unoccupied males was 583, and was therefore 62 in excess of the figure for 1890-92, the figure for unoccupied males being as before stated, 175 only.

Hitherto, no serious attempt has been made to deal in comprehensive fashion with the occupational mortality of females. Having regard, however, to the vastly increasing importance now attaching to female industries, especially

those carried on under the earliest of the Factory Acts, a determined attempt was made in connection with the recent Census to do something in this direction.

As a result of long and patient work, in the course of which experiments were made with a large mass of figures bearing on the question of female mortality, it was found impossible to arrive at useful information on this most important subject. The uncertainty attaching to the statement of occupations in the death register in the case of females rendered futile any attempt to deduce reliable conclusions therefrom. In fact, the rates which were obtained in the course of our lengthy inquiry were such that no responsible person would publish them. The truth is, that the machinery of an ordinary Census is quite unsuitable for the purpose. If any results worth using are to be obtained, they can only be achieved by means of an industrial census, conducted by enumerators specially qualified for the work.

In the accompanying Table is given a list of the principal occupations which impose on the workers exceptional tendency to fatal phthisis.

Occupation.	Comparative Mortality Figure.
Occupied Males.	175.
Tin-miners	838
Inn, hotel-servant (London)	669
General labourer (Industrial Districts)	571
Inn, hotel-servant (England and Wales)	533
General labourer (London)	531
Cutler, scissors-maker	516
Costermonger, hawker	516
Copper-miner	501
General labourer (England and Wales)	450
Innkeeper, servant, etc. (London)	443
Inn, hotel-servant (Industrial District)	428
Do. do. (Agricultural District)	410
File-maker	375
Messenger, porter	368
Tool, scissors, file-maker	353
General shopkeeper	344
Lead-miner	317
Brush-maker	314

In this list will be found several occupations in which the comparative mortality figure for phthisis greatly exceeds the average for occupied males generally. Tin-miners head this list, their comparative mortality figure being no less than 838, or more than four times the rate to which occupied males in the aggregate are subject. The mortality among tin-miners in 1900-02 showed a serious

increase on that of 1890-92, but it should be stated that the rates are based on a comparatively small body of men, and that the number so employed in the counties of Devon and Cornwall (the home of tin-mining in England) is steadily diminishing. Next in order of phthisis mortality comes the London inn and hotel-servant, whose mortality figure is 669, or more than three times that of other occupations. Exceptionally heavy phthisis mortality is by no means limited to inn-servants in the *metropolis*. In the *industrial* districts they sustain a phthisis mortality figure of 428, and even in the *agricultural districts* the figure is 410: in both cases considerably more than double the rate obtaining in other occupations. The mortality in this class scarcely differs from what it was ten years ago.

Next in order come general labourers, with a mortality figure of 571; the same class in London with a figure of 531; costermongers, 516, and so on.

Among the occupations that entail heavy phthisical mortality are a few in which the workers are exposed, in exceptional degree, to dust and irritating vapours of various kinds.

Among cutlers phthisis makes terrible havoc—their mortality figure is 516, which is higher than it was ten years ago by 134. According to previous accounts it appears that the mortality of cutlers is increasing as years go on; not from phthisis alone, but from several other diseases that seem to prove the unhealthiness of their occupation.

As with cutlers, so with *file-cutters*—their mortality is appalling. Their comparative mortality figure from phthisis is 375; and although this is less than in 1890-2, it is considerably higher than in the years 1880-2 and 1890-2.

Glassworkers are an unhealthy class of men, whose occupation exposes them to extremes of temperature, a condition very likely to induce habits of intemperance. Their mortality figure for phthisis is 265, but this is less than it had been in 1890-2 by 22 per cent.

The mining industry is one, the statistics of which have been carefully examined in connection with the recent, as well as with the two previous, Censuses. The number of men over fifteen years of age employed in this occupation in England considerably exceeds half a million, and this number is probably still increasing. Although the nature of their avocation exposes them in an exceptional degree to variations in temperature, and to the inhalation of dust

of various kinds, miners are not (with a few exceptions) particularly prone to phthisis, although their mortality figure for respiratory diseases other than phthisis is generally excessive.

The mining industry sustains a mortality figure from phthisis considerably lower than that of other occupations —it averages only 96, and has decreased by 31 since 1890-2. Copper-miners, tin-miners, and lead-miners are, however exceptions to this rule, for their mortality figures from phthisis are 501, 838, and 317 respectively, and the figures for two out of the three are considerably higher now than they were ten years ago.

I will not weary you, gentlemen, by going through the entire list of occupations to record their relative liability to phthisis, nor can I do so satisfactorily at the present moment, because the rates in some of the occupations have not been finally checked. When, however, this present Address appears in print, you will be in possession, provisionally, of all the information on occupational mortality that we have been able to derive from the recent Census, and from the half million or so of deaths which have been examined for the purpose.

As a whole the records show an improvement on those of ten years ago, and as such I hope they will be interesting to students of vital statistics.

THE DISTRIBUTION AND NATURE OF SPRUE, WITH NOTES ON THE PATHOLOGY OF INTESTINAL DYSCRASIAS.

By W. CARNEGIE BROWN, M.D., M.R.C.P.

(*Read December 14th*, 1906.)

I PROPOSE to-night to submit for your consideration a few remarks on the prevalence and general features of sprue, viewed principally as an intestinal auto-intoxication; and to compare it with some other toxæmias, to which an intestinal origin has been assigned. Of recent years sprue has been responsible for a very large mortality, and a yet larger rate of permanent invalidism among Europeans in Eastern Asia; and as it still continues to spread, I conceive that no apology is necessary for asking your attention to this disorder of the Eastern tropics. To a Society such as this, whose purview of disease is determined, not by its geographical limits, but rather by its influence on the welfare and destinies of all races of men, and which has taken such a prominent interest in the elucidation of the problems of tropical medicines, this study would seen to be peculiarly germane; and in approaching it I have only two regrets: one, that the duty of opening the discussion should not have been entrusted to an abler exponent; and the other, that the regulations for our proceedings restrict me to an altogether inadequate thirty minutes in which to do it.

To residents of the Eastern tropics, and more especially to the Europeans who are now colonising them in such numbers, sprue has assumed a position of very definite importance. Its increase and extension will scarcely be credited. Undescribed, unknown, and probably almost non-existent fifty years ago, it is now so prevalent in some of the settlements and seaports of our Eastern possessions, that it has been computed that at least half of all the Europeans who have had fifteen years' residence are more or less seriously affected. And this exceptional incidence and liability to contract the disorder

increase proportionately with the extension of tropical service.

For many reasons, but especially from the fact that the disease has not been clearly understood, and that deaths from sprue have been assigned to other causes, accurate statistics of its prevalence are not available; but some idea of its extent and severity may be formed from the circumstance that an estimate by a reliable authority places the number of deaths and invalidings in the French Army and Navy in Cochin China, since its occupation by these forces, at not less than forty thousand. Though the mortality in the Dutch Indies has been somewhat less, owing probably to the fact that a large proportion of the troops are not of unmixed European birth, it has still been very high, and Java and Sumatra are particularly affected. In these places, too, but to a less extent, the civil population has suffered severely.

Sprue has shared a disadvantage that attaches to most of the so-called "new" diseases, in having had to submit to the imposition of many different names; but the term "Sprue," by which it was originally described, when definitely differentiated, appears to be better than any of those that have so far been suggested. It is distinctive and characteristic; it implies no rigid canons of pathology or of geographical prevalence, and—what is, perhaps, its strongest claim to general adoption—it has already received the sanction of widespread acceptation.

If I am to leave myself sufficient time to speak of the epidemiological aspects of sprue, and, especially, if I am to speak of it as a type of a numerous and infinitely varied group of tropical diseases—which, perhaps, it might be preferable to term syndromes—that illustrate, better than any disorders seen in temperate climates, the phenomena and the morbid processes of intestinal auto-intoxication, it will be impossible for me to say anything of its symptoms or diagnosis. These are, no doubt, from description at least, familiar enough to you all; and I will only say, in speaking of its differentiation, that the disease which has been variously described as tropical aphthae, white chronic tropical diarrhœa, Ceylon sore mouth, scorbutic diarrhœa, endemic entero-colitis, chronic enteritis of Indo-China, etc., is the only one which I include under the term, and that other disorders, such as white flux, famine diarrhœa, hill diarrhœa, etc., are not accepted as being sprue.

Sprue is of peculiar interest to epidemiologists in that it is a characteristic type of regional, as opposed

to climatic, disease. That is to say, it is seen only in persons who have lived within a certain well-defined area; beyond the limits of that area, it is, practically, unknown. Endemic and widely prevalent in the countries of its preference, in regions of similar latitude and atmospheric conditions, it does not occur. Like yellow fever, and certain other exotic diseases, it has its own *foyer*, but unlike them it has never spread in epidemic form. It has spread, and spread rapidly; but, essentially a tropical disease, it is peculiar in that its tendency has been to diffuse itself north and south, rather than along the equatorial parallels. In the Malay peninsula, it is perhaps the most prevalent of all the many serious intestinal disorders to which Europeans are liable; yet in countries of like latitude and climate, as, for instance, the tropical States of America and Africa, it is seldom, if ever, seen. In North and South China, in Cochin China, in Java, and the East Indian islands, it is extremely prevalent, but it does not contribute to the mortality returns of Mexico, Florida, or the West Indies. It is further peculiar that, though a disease apparently identical with sprue was described by Hillary, of Jamaica, a hundred and fifty years ago, as being not uncommon there, nothing now seems to be known of it in that island. I am aware that cases have from time to time been reported from various places; but it is questionable, in my opinion, whether genuine sprue ever originates in any part of the world except the tropical and sub-tropical regions of Eastern Asia. The focus of the disease is to be found within a rough circle which has Singapore for a centre, and which embraces the Malay peninsula, Annam, Siam, Java, and Sumatra. From this region it has been diffused westwards and northwards to Ceylon, India, and Burmah; eastwards and northwards to China; and eastwards and southwards to North Australia, New Caledonia, and the Fiji Islands. Sprue is further peculiar in that, although extension has taken place mostly along the trade routes to the sea-ports, it has accurate racial and geographical limits. It does not, for instance, affect the native populations of the *Hinterlands*—so far as we know, it is co-terminous with European settlements—and, though prevalent in Shanghai, Borneo, and the Philippines, it is very rare in Japan.

Within this large area there are considerable variations of climate. Sprue is propagated with equal vigour in all of them. It flourishes in the cool upland atmosphere of the hills and patnas of Java and Ceylon, in the perennial

moist heat of the alluvial littoral in the Malay peninsula, in the seasonal extreme temperatures of North China. But it is at least probable that great heat and moisture are essential factors in its causation, and that, though the disease not infrequently appears to originate in the hills, the actual infection of sprue is conveyed in the plains. Be this as it may, it is certain that only those who have been exposed to very high temperatures acquire the disease; that its favourite habitats are subject to the heavy rains of alternating monsoons; and that clinical experience seems to confirm the belief that, though in places with well-marked seasons it is less prevalent, the type is there more malignant.

Sprue is common to both sexes. Females are affected equally with males. European ladies, who have been the subjects of anæmia or chlorosis, are in middle life particularly liable to attack.

Sprue is usually seen as a disease of mature years. It is exceptional to meet with it in Europeans before the age of thirty-five, and it seldom declares itself till after forty. But this characteristic is obviously due to the circumstance that their tropical life does not generally commence before they are adults, and that only those of them who have had a considerable period of residence—fifteen to twenty years—are prone to attack. In young adolescents, born of white parents, and reared in the tropics, a class peculiarly subject to disorders of a degenerative tendency, sprue is by no means uncommon. In the Malay peninsula, Eurasians, a numerous and generally healthy community of mixed parentage, who are mostly of Portuguese descent, are frequently affected; and in them, too, it occurs at all periods of life after the age of puberty Their long settlement, as East Indian colonists, might have been expected to make them to some extent refractory to climatic disease; but, as a matter of fact, they are extremely liable to malaria, and their susceptibility to sprue, though greater than that of the native races, is less than that of Europeans. It is, further, peculiar that in the matter of liability to disease, the Caucasian element of their parentage appears to predominate, and that their tendency is to acquire the maladies of the European rather than those of the Oriental. Sprue does not occur in infants or children, but in advanced age it is very common. Consequent, doubtless, on the combination of its own degenerative processes with the debasement of tissue incident to senility, sprue is then

apt to assume a severe type, and its progress is retrograde and rapid.

Proportionately to their numbers, Europeans suffer much more severely than other races. Natives are by no means exempt, but sprue is, pre-eminently, a white man's disease. In the area which has been indicated as its original home, the population is largely alien. Extensive immigration has taken place, both from East and West, and the incidence of sprue is proportional to the capacity for acclimatisation that is possessed by the various peoples. In this respect, indeed, a clear line of distinction is further drawn between sprue and the more acute intestinal affections. These latter affect all settlers indifferently, and furnish a copious contribution to the total death-rate; and though it is the case that sprue is occasionally seen in an acute and extremely fatal form, its pathological characters are widely separated from those of enteritis and dysentery. The Malay, indigenous for some four hundred years, is little if at all affected by sprue. Chinese, who during the last two centuries have immigrated in enormous numbers, to work as miners and agriculturists in these productive lands, who have largely adopted the customs of the country, and of whom a large proportion are now to all intents natives, enjoy an almost equal degree of immunity; Arabs, Tamils, and other immigrants from India and Western Asia, acquire it somewhat more severely. But it is one of the many peculiarities of sprue that the full strength of its infective force is seen only in Europeans. The explanation of this pronounced race predilection is by no means easy, but the fact is an established and prominent one. Probably no two affections afford a better illustration of the peculiarities of racial predisposition than beri-beri and sprue. Both distinctively diseases of the Eastern tropics, both so prevalent in certain places as to be, for the peoples of their selection, almost incidents of residence, the difference in their preference for the Mongolian and the Caucasian is as marked as the divergence of their symptoms. In the open alluvial workings of a tin mine in the East Indies, all the employés are exposed to the same atmospheric conditions, to the sun, to the rains, and to the close humid air of the jungle. The Chinese coolie is stricken with beri-beri, his European overseer with sprue. In no essential condition, even in that of diet, do the circumstances of their daily life differ. Further, though in other places beri-beri frequently attacks Europeans—*e.g.*, in the Dutch Army of Occupation in Acheen, and on board

ship—in the Malay peninsula the overseer never gets beri-beri, the coolie never gets sprue. We have here, manifestly, strong presumptive evidence that capacity to acquire a particular disease is inherent in a race; and that the European constitution offers the most favourable conditions to the acquisition and development of sprue.

Had time permitted, I would have described the symptomatology and morbid anatomy of sprue, and the various theories of the disease that have been founded on them; but I must content myself with a comparison of its more prominent features with those of progressive pernicious anæmia, a presumed, and anchylostomiasis, a typical, intestinal auto-intoxication, which I have arranged in tabular form, and to which, at your leisure, I would ask your attention.

You are all familiar with the generally-described symptoms of sprue: the lesions in the mouth, the dyspepsia, the diarrhœa, the abundant and colourless fæces, the undulating and relapsing tendency, and it is unnecessary to say anything of them; but the toxæmia of sprue, which appears concurrently with the atrophy and degeneration of the intestinal mucosa, seems to be of such definite importance, that to speak of the disease at all without giving it some consideration would be impossible.

Clearly, this irritable and unsettled condition of the alimentary tube—this phenomenal abundance of its dejecta, indicate a failure of normal absorption; but there is also much clinical evidence that we have in sprue not merely a failure, but also a striking instance of perversion of the absorptive function in nutrition. Toxins are absorbed, while the nutritious elements of the chyme are rejected, and pass away in the copious excreta which are such a marked clinical feature of the disorder. It cannot be too strongly insisted that sprue is by no means a mere arrest of nutrition; it is a definite and distinct toxæmia; and it is characterised by a marasmus closely akin to the cachexiæ of pernicious anæmia, anchylostomiasis, and other diseases, in while toxins are continuously generated by a definite agency, and reabsorbed into the systemic circulation.

With the advent of toxæmia, failure of nutrition is, of course, conspicuous; it comes on insidiously and gradually; so much so, that it may scarcely be noticed for two to three months after the dejecta have become colourless; but, sooner or later, it is found that the

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patient is losing flesh. His skin is flabby and loose; his muscles soft and smaller than usual; those of the upper arm, notably the deltoid and biceps, and of the calf, being especially lax and shrunken. The subcutaneous fat is diminished, and the connective tissue feels empty and inelastic. There is always loss of weight; sometimes it is insignificant, but in most cases it is considerable, and occasionally it is very great. On further investigation, it is found that there is anæmia, and that it is of a definite kind. The blood coagulates slowly; there is marked diminution in the number of the red-blood corpuscles—usually to two or three millions per cubic millimetre—and there is an increase in hæmoglobin. The colour index is high. There is no poikilocytosis, no vacuolated or nucleated red cells. If we accept the differentiation of Cabot, the type of anæmia is therefore secondary, and indicative of an intoxication. It is, indeed, such as might be expected to follow the absorption of a toxin which directly destroys the corpuscles in the circulation; and is akin to that seen in lead and arsenic poisoning, chronic dysentery, cirrhosis of the liver, and anchylostomiasis.

Relatively to red corpuscles, the leucocytes are considerably augmented in numbers, the proportion being about 1 to 400. There is, however, no absolute leucocytosis; on the contrary, the white cells would appear to be somewhat reduced, averaging 6000 per cubic millimetre. The relative proportion of large mononuclear and eosinophile cells is greater; of polymorphonuclear, less than normal; while lymphocytes remain about normal. An average of twenty-two differential counts, in different cases, in which there was no history of malaria, gave:—

Polymorphonuclear	56 per cent.
Large mononuclear	18 „
Lymphocytes	20 „
Eosinophiles	8 „

So far as I can ascertain, the results of blood counts are not influenced by the return of the patient to a colder climate, and the absolute and relative changes persist throughout the whole course of the disorder.

Like other symptoms of advanced sprue, the marasmus peculiar to the disorder is characteristic and unmistakable. The complexion is sallow and muddy, the expression listless and careworn, the eyes dull, the sclerotics dirty white. There is a tendency to patchy pigmentation, notably below

the clavicles, between the scapulæ, on the nates, and on the interior aspect of the thighs. There is marked disinclination for exertion, and lassitude is intense.

The urine is scanty, high-coloured, and loaded with urates. The pulse is usually slow and soft, frequently intermittent or irregular, occasionally rapid, always of very low tension. The skin reflexes are frequently abolished; the deep are sluggish, and of diminished excitability. Though the rest of the body may feel uncomfortably hot, and perspiration be excessive, the feet and hands are cold and clammy.

In neglected and unfavourable cases these symptoms are accentuated. Listlessness passes into apathy; the skin hangs loose and flaccid; bed-sores form readily. The lips are dry and cracked, often covered with sordes and aphthae. The circulation weakens; the pulse increases in frequency, and shows marked irregularity and lack of force; generally there is albuminuria and œdema of the feet. Soon the abdomen becomes more inflated; the diarrhœa is excessive, watery or choleraic in character, and indicative of total failure of digestive power. With the approach of death the prostration is augmented, the distension of the abdomen subsides, and the purging ceases. The vital powers are gradually lowered until they are exhausted; and the fatal termination is the result of heart failure, the patient usually retaining his mental faculties to the last.

This, however, even without treatment, is happily not the invariable termination of sprue. A considerable proportion of cases pass into a latent condition, and though always liable to gastro-intestinal derangements, the patients enjoy fairly good health, and live frequently for many years without any symptoms of toxæmia. In a still larger number of the cases that are left untreated, the disorder is protracted indefinitely; its urgency at times abating, at times increasing. But when toxæmia is once established, if treatment is not prompt and effective, there is little hope of averting a fatal issue. It is not too much to say that the patient's life depends on its early recognition; and that its importance, as an indication for prognosis and treatment, cannot be exaggerated.

Here, then, is a picture—a picture in which the lights and shadows are in prominent contrast, and in which the principal phenomena and incidents stand out in bold relief—of a disease which is a typical example of intestinal auto-intoxication; and we ask ourselves: "Has the pathology of this somewhat obscure tropical disorder no light to

throw on that still more obscure morbid process? Or does what we know of intestinal toxæmia help us to understand the symptoms, and perhaps to better our ideas of treatment in sprue?

The only conclusion that it seems possible to deduce from the symptoms and morbid anatomy is that the disorder is due to a specific bacterial infection, which gradually spreads from the mouth through the alimentary canal. Doubtless this invasion is, from the first, attended by the elaboration of specific toxins; but while the disease is confined to the upper part of the digestive tract, they are neutralised, or fail to gain access to the circulation. At all events, there is no toxæmia, and apparently only in the later stages is it possible. It is for the pathologist to consider whether the evidence that can be adduced in support of the hypothesis of specific infection is sufficient to establish the claim; and if it is admitted, to investigate the possible methods of absorption, and the resistance which is naturally offered to it. He has further to decide whether the theory of bacterial invasion adequately accounts for the symptoms, and whether it offers a satisfactory explanation of the absence of colour in the dejecta.

The ultimate solution of these questions must depend on improved bacteriology of the intestinal canal, but in the meantime no other explanation than that they are evidence of a definite microbial infection seems to be compatible with the actual morbid phenomena of sprue. The preliminary invasion of the mouth, its chronicity, its constant and definite characters, the submucous infiltration and congestion, and especially the gradual and progressive extension, are otherwise inexplicable. And so through the stomach and intestines; no other theory will satisfactorily explain the peculiar inflammatory change, the ulceration, the glandular reaction: intestinal lesions such as these of sprue are seen only as a result of microbial growth, and are never seen, so far as we know, without it; and in such widely separated morbid processes as tubercle, where it is certain, summer diarrhœa, and dysentery, where it may safely be presumed, their character is altogether similar. Further support to this view is given by the geographical distribution of sprue; its prevalence within a definite area, its conveyance and extension, and by the fact that in regions with climates that are identical, it is unknown. That sprue is a specific infection, and not merely an absorption of toxins naturally present, is perhaps still more

difficult of proof; but there is much also to support the former contention, if we bear in mind that the initial morbid process is in the mouth and not in the intestine; that the endemicity of the disorder is limited and accurately defined; and, further, that in its area of prevalence the climatic conditions vary widely. Were loss of resistance due merely to a prolonged residence in a high temperature, there would seem to be no reason why sprue should not be as common, say, in Central America as in Malaya; or why it should be as prevalent in Shanghai as in Singapore; and it is on these grounds I venture to submit that there is sufficient reason to believe that the disorder is not merely an expression of deterioration, and that the specific bacterial origin of sprue is more than a reasonable assumption.

That being granted, there remains the question of toxæmia. Let it be admitted that there is bacterial growth, and that the very definite form of toxæmia which we see in sprue is due to absorption of its toxins, we have then to ask: Are these toxins elaborated by that bacterial increase in the walls of the alimentary canal or are they the result of growth in its lumen? Do they have to traverse the lining epithelium, and is their passage facilitated by its shedding and destruction? Again, are they "normal" or "abnormal"; and, yet again, to what, in natural conditions, are resistance and immunity due?

No problem in internal medicine offers so many difficulties as that which is presented for solution by infections from the intestinal canal; and of recent years the *rôle* that has been assigned to disorder of its function in the production of general dyscrasias of widely different types has been extended and emphasised by much careful and scientific work, both at the bedside and in the pathological laboratory. There is now a large body of evidence that numerous diseases—which, to take only those which I have already instanced—like progressive pernicious anæmia, were long believed to have their origin and pathogenic field solely in the hæmopoietic system; or, like anchylostomiasis, in the direct abstraction of vital elements from the circulation, are in reality the manifestations of the absorption of toxins which are generated in the alimentary canal.

The possibility of intestinal auto-intoxication has long been a favourite subject of vague and speculative theory, though it is only since Hunter published the result of his researches on pernicious anæmia that attention has been

seriously directed to it as a possible origin of specific dyscrasias.

Much has since been written, but perhaps the publication of Metchnikoff's "Études sur la Nature Humaine," that graphic and complete demonstration of observed fact and deduced conclusion, which is read with equal profit by layman and scientist alike, and a recent Report by Professor Hamilton, of Aberdeen, to the Board of Agriculture and Fisheries on certain diseases of the sheep, mark the most important epochs in the literature of the subject.

The list of disorders which, with more or less assurance, we now include in the number of those that operate by intestinal auto-infection, is a long one. In the case of some of them there can be comparative certainty. It is obvious enough, for instance, to those who are familiar with the general dyscrasia which is a result of chronic dysentery, that the fatal issue in that disease, no less than in degenerative atony of the colon, is due, in some part, to exhaustion caused by the intestinal lesions, but in a far greater measure to the auto-intoxication which results from the absorption of intestinal toxins. The pathology of other disorders in the list is, however, more conjectural. It has recently been claimed—and the claim is supported by observations of high scientific value—that that protean dyscrasia, beri-beri, is but the systemic indication of absorbed microbial products generated during a bacterial invasion of the duodenal mucosa. Whether that theory—for it is still only a theory—be ultimately confirmed as the true pathology of the disease or not, the affinity of the alleged morbific process to that which has been demonstrated in chorea paralytica of the sheep is sufficiently striking. Much evidence, too, has recently been adduced by clinicians, that the numerous disorders hitherto grouped together as blood diseases, such as splenic anæmia, chlorosis, and the different leukæmias, originate in intestinal infection. But the pursuit of theories as to the pathogenesis of these ailments, and of other widely-differentiated morbid processes, which, like Banti's disease, cirrhosis of the liver, and other visceral degenerations, have fallen under grave suspicion, is though a fascinating as yet only a speculative study; and, apart from the question of the time which we have at our disposal to-night, is one that with the still limited knowledge which we possess of the physiology and pathology of digestion, may easily lead us too far afield. I propose, therefore, as far as possible, to confine myself to ground

that may be regarded as reasonably sure, and to limit my observations to the consideration of what may be the process of infection in a concrete instance of intestinal auto-intoxication such as we find in sprue.

In the bacteriology of the human alimentary canal, the prominent facts are as follows:—

First, that we have a tube, in the lower half of which, at least, swarms of parasitic micro-organisms, normally proliferate in such inconceivable numbers that no term of computation can ever furnish an expression of their quantity; secondly, that though they develop and reproduce in closest contact with its mucosa, continually soaking it in their secretions, neither they nor their toxins, under ordinary circumstances, find opportunity to enter the circulation, the portals of which stand so widely open to legitimate nutriment; and, thirdly, that after death, and in the course of various diseases, and perhaps under some other exceptional conditions, a small proportion of them, or of one variety of them, do penetrate the mucosa and gain access to the systemic vessels. The question arises: To what is the natural impermeability due? Is it to phagocytic protection? Do masses of leucocytes, lying somewhere in the coats and follicles of the intestine, intercept and destroy them? There is no evidence that any considerable part of the protection is due to leucocytic activity. In the first place, no actual phagocytosis has, under normal conditions, been actually observed, though careful search has been made for it. Further, were protection due to phagocytosis, we would expect to find in the human intestine, instead of disconnected and rudimentary patches, large and continuous masses of lymphoid tissue, such as are to be seen in rabbits and other animals of the same genus. As a matter of fact, leucocytes are by no means numerous, in normal conditions, in the intestinal walls; while we can scarcely believe that the bacterial life of the human alimentary canal is less abundant or virulent than that of rodents.

Considerable light has been shed on the whole question of intestinal infection by the publication of a report on some recent researches by Professor Hamilton, and a committee associated with him, into the ætiology of certain diseases of the sheep. They have shown, among other important results, that a highly fatal disorder, known formerly as "louping-ill," and now, more scientifically, named chorea paralytica ovis, is a typical intestinal auto-intoxication, and that the condition of the blood is the most

important factor in its development. They have further shown that this condition is periodic; that in spring, the only time when the disease is prevalent, the blood forms a favourable culture medium for the development of the specific bacillus; and that, at other times, it is not only inimical but actually bacteriolytic to it. They have also demonstrated that this quality of the blood can be artificially induced, and sheep made immune to the disease by administering to them, during the non-susceptible months, large quantities of virulent cultures of the specific bacillus, the minutest doses of which, in susceptible months, are fatal. Phagocytosis was directly excluded by repeated observation. To follow the details of this important and most interesting research would exceed the limits of our time, and for particulars I must refer you to Professor Hamilton's Report to the Board of Agriculture and Fisheries (1906); but the propositions that may be regarded as established by him are: That the disease, and others of the same group, are intestinal auto-intoxications, caused by a specific anærobic sporing bacillus, which gains entrance to the alimentary canal by the mouth, and develops in extraordinary numbers in the intestinal mucosa; that, in susceptible months, the bacillus is able to penetrate the coats of the gut to the peritoneal sac, in the secretion and on the epithelium of which it finds a highly favourable medium for its development; that its growth there is followed by definite and fatal symptoms of auto-intoxication, and that, in unfavourable months, it cannot so pass through. By actual experiment, Hamilton has shown that this inhibition is effected by bacteriolysis, and that during susceptible months the bactericidal power of the blood is lost. Further, it is shown that, the difference between acute and chronic cases depends on the rapidity and volume with which the bacillus effects its passage; that it is due, in other words, to the extent of the loss of that power.

As aids to the solution of some of the problems of intestinal intoxication, these facts are of much significance. Granted that in the sheep the blood has wide seasonal variations in bacteriolytic power, it can scarcely be otherwise in man; and an entirely new conception, not only of periodic susceptibility to disease, but also of climatic, race, sex and age preferences, which have hitherto remained entirely unaccountable and unexplained, is formulated.

Without going so far as to say that pernicious anæmia, or sprue, or anchylostomiasis are closely analogous to chorea paralytica of sheep, it is obvious that the lines on which

they operate to the detriment of the organism may well be the same, and that the powerful hæmolytic action possessed by their toxins operates in a manner that is precisely similar.

This demonstration of the pathogenic processes in chorea paralytica ovis and other similar affections is, of course, not a complete explanation of all the phenomena of intestinal infections; still less can it be said as yet to afford much assistance in their prophylaxis or treatment in man; but as a definite indication of the importance of external conditions in influencing the functions of the blood, and of the lines on which future work must proceed, its importance will not readily be over-estimated. Our conception of the pathology of sprue among other diseases must be modified; it is now probable that the constitutional and fatal symptoms of all intestinal toxæmias are to be ascribed, not to the direct effect of hostile microbial life, but to the loss of resistance in the blood, which allows it to penetrate the intestine. An important part of the demonstration is that of the *rôle* of the peritoneal cavity in such an infection; and the view that, not until the bacteria have effected a lodgment and developed there, is toxæmia possible, is at least supported by the clinical fact that in sprue the advent of toxæmia coincides with the proximity of the lesions to the peritoneal cavity.

Not the least remarkable also of the many remarkable results of this research is the indication that it is of little importance whether these microbes are normal denizens of the alimentary canal or not. As a matter of fact, as Hamilton further points out (in an article published in a volume of Quatercentary studies by the University of Aberdeen) that other organisms—all of them also apparently, anærobes—which possess hæmolytic powers of high intensity, are naturally present in enormous numbers in the intestinal canal, and that, under ordinary circumstances, they flourish there innocuously. In his classic work on pernicious anæmia, Hunter, though impugning a mouth streptococcus, was careful not to definitely incriminate it, or to exclude the possibility of that disease being due to a micro-organism which was ordinarily a harmless and perhaps beneficent parasite. The "normal" bacteria of the human intestine have, indeed, long been suspect, and recent criticism of Hunter's work has been directed rather against the identity of his supposed specific microbe, than against his theory of intestinal auto-intoxication, which is now, I think, undisputed. Professor

Hamilton states that in progressive pernicious anæmia he has found a bacillus which he regards as pathogenic—an anærobe with a growth, be it noted, of an intensely acid reaction, and secreting toxins of proved hæmolytic virulence; but he regards the pathology of the disease as turning, not so much on whether the bacillus is specific or not, as on the power of the intestinal wall to inhibit the penetration of its denizens into bacteriolysing blood.

In pernicious anæmia we have no clinical facts which justify the assumption of a pathogenic microbe introduced from without. The changes in the marrow avail us nothing, for they are, most probably, merely compensatory —an hypertrophy for increased hæmogenic effect—and we know that bone marrow given as a remedial agent has no beneficial action. The cleansing of the intestinal canal by purgatives is of much value in chlorosis; and though its value has not been shown in pernicious anæmia, that is due to the fact that in that disease the toxins are already in the circulation and beyond its reach. Probably, both disorders are due to an identical auto-intoxication, and their differences in intensity, both as between each other and as between different cases of the same disease, indicate rather that there is a different resistance in the blood plasma to one single toxin than that there are more than one. There is, too, in sprue and other anæmias little justification for their subdivision on a basis of whether corpuscles or hæmoglobin have suffered most; they merge imperceptibly into each other, and clinical and bacteriological analogies suggest that they are only varying degrees of hæmolytic intestinal infection, possibly by one toxin, probably by more than one.

The case of anchylostomiasis is somewhat different. Though, as has been asserted, it is possible that a special bacterial growth is started in the intestinal canal by the invasion of the grosser parasite, it has been shown by experiment that the anchylostomum can, and does, itself elaborate toxins which have a direct hæmolysing influence on the blood, and it is certain that the peculiar symptoms of the disease are a uniform result of their absorption. But it is also certain—and the fact is an important one as corroboration of these views of intestinal auto-intoxication —that absorption does not take place at once, or of necessity. We know that there may be a considerable infection without anchylostomiasis; in certain parts of the tropics, at least, it is not unusual to find many anchylostoma —perhaps two or three hundred—in the intestines of persons

who had shown no symptom of anchylostomiasis during life. It would seem to be the case that considerable quantities of toxin may be shed into the intestine without consequent absorption, and that special conditions are necessary for that to take place.

There is no richer mine of clinical material for the illustration of toxin absorption from the alimentary tube than is to be found in the field of tropical medicine. To name only one or two exotic disorders. Asiatic cholera is a typical example of its acute form. The evidence that it is a true toxæmia, and not merely an intense local irritation, is furnished in some part by the results of hypodermic injection of cultures of the specific spirillum, but chiefly by its clinical manifestations; by the fact that the prostration and collapse are inadequately explained as results of purging and vomiting; by the muscular cramps, by the suppression of urine, and largely by its close resemblance to other undoubted toxæmias, to ptomaine poisoning, to acute trichinosis, and to the choleriform *accès pernicieux* of malaria. There can, besides, be little doubt that there is a normal blood resistance. The spirillum, we know, may be ingested without ill effect; its entrance is a necessary condition, but it is not the only condition in the production of cholera; and, further, there is no evidence whatever that the failure of antagonism is dependent on catarrh of the mucosa, or any local abnormal state. On the other hand, there is strong presumption that, in common with other intestinal auto-intoxications, protection is secured by the blood itself, and that it depends on whether the condition of that fluid is one of receptivity or repulsion. In Asiatic cholera the multiplication of the spirillum is so rapid, the production of toxins so excessive, that by the very intensity of their virulence and quantity the inhibitive power of the blood is paralysed, and the evidence of toxæmia obscured by the urgency of the symptoms which they have produced.

In the case of acute dysentery, though its bacterial origin may safely be presumed, we are on less assured ground. But it, too, would seem to afford an example of a toxæmia which, although overshadowed by the severity of the local symptoms, and the exhaustion of which they are obviously the cause, is still prominent and unmistakeable. The high fever which marks the initial stages indicates not only the absorption of a toxin, but also something of its nature, in the fact that its action, as opposed to that of

cholera, is sufficiently slow to give time for a febrile reaction. In this regard, also, it is perhaps worthy of note that in acute dysentery the symptoms are frequently disproportionate to the intestinal lesions, and that their severity is lessened by the administration of purgatives, and presumable consequent cleansing of the intestinal tract. The decrease in resistance to dysenteric infection, which is so notable in armies in the field, during periods of famine in the tropics, and in asylums, is, too, more readily—and perhaps indeed only—explicable by a theory of alteration in the inhibitive power of the blood.

In chronic dysentery, whether amœbic or bacterial, toxæmia is always a marked feature. It is closely allied to the toxæmia of sprue; so much so, that it is due as much to the similarity of their constitutional symptoms as to their morbid anatomy that the view, still so widely held by French physicians, that they are identical, is based.

I am afraid that at this point I must take leave of these problems. Had there been time I would have wished, still by the guidance of these later researches, to follow the inquiry somewhat further, and to have asked your attention to other forms of toxæmia, some of whch I have instanced, and to the evidence for connecting them with the hæmolytic properties of so-called normal anærobes of the alimentary canal: to have examined the results that have recently been attained in the study of the bacilli associated with dysentery and summer diarrhœa, and their connection with auto-intoxication: and to have adduced some further clinical evidence as to the nature of sprue and other allied diseases, which is to be obtained from the results of treatment; but my time has come to its close, and with these few fragmentary and disconnected facts and theories, I must leave the subject in your hands.

Discussion on Dr. Carnegie Brown's Paper.

The President: I am sure we have all listened with much pleasure to this Paper, concerning a disease which, fortunately for us, is not indigenous to this conntry. There are several gentlemen present who, I am quite sure, will be glad to discuss this paper, but I should like, if I may, to ask Dr. Carnegie Brown if he can tell us something as to the treatment of the disease. He speaks of treatment as being more or less successful, but, as far as I can remember, he did not give any details of it.

SIR PATRICK MANSON: Although we know of the existence of a condition designated "sprue," we are still in doubt as to its causes, characteristics, and exact nature. I think on the latter account the Society is particularly indebted to Dr. Carnegie Brown for venturing to bring forward the subject.

I wish he had attempted at the outset of his Paper to furnish a definition of sprue. There are so many diseases of the alimentary canal in tropical countries which, having two or three symptoms in common, are apt to be confounded. For example, we talk of dysentery as if it were a single disease; we talk of diarrhœa in the same way; and we talk of "sprue" as if it too were a single well-defined disease. Now these expressions indicate certain combinations of symptoms in disease affecting particular organs; they do not indicate the kind of disease, they give us no clue to the specific character of the malady.

"Dysentery," for example, indicates half a dozen different diseases, including several kinds of protozoal dysentery, several kinds of verminous dysentery, and probably several kinds of what is called bacilliary dysentery; and possibly many other diseases, whose common pathological characteristic is inflammation of the mucous membrane of the great intestine. There may be a dozen different causes for inflammation of the skin; so I believe in the case of the intestinal canal there may be a dozen different causes for inflammation of its mucosa. In each case there may be a dozen different causes which produce the same or a similar result. Nevertheless, the pathological results of these different causes are really different diseases, each requiring a definite and distinct treatment, prophylaxis and management. I rather regret, therefore, that Dr. Carnegie Brown has not formulated more definitely what he means by the word "sprue," both as regards symptoms and etiology. Perhaps I might supplement what he said by attempting a symptom definition. I might say that sprue is a chronic form of catarrhal inflammation of the mucous membranes of the alimentary tract from mouth to anus, characterised by periods of quiescence and exacerbation, recurring attacks of superficial ulceration of the tongue, probably ulceration of the œsophagus and, inferentially, of the stomach and the rest of the alimentary tract. It is especially characterised by a peculiar type of diarrhœa, the formation of a large quantity of intestinal gas, by stools abnormally profuse as regards quantity, remarkably pale as regards colour, and filled with minute air-bubbles. If

untreated, the disease almost certainly progresses towards a fatal issue; but if treated at a sufficiently early stage on proper lines, it almost certainly terminates in temporary recovery, but with a marked tendency to relapse. That is the symptom group I understand by the word "sprue." Whether that definition coincides exactly with Dr. Carnegie Brown's conception of the disease, I do not quite know.

Dr. Carnegie Brown has advanced a statement as regards the geographical distribution of sprue which is very interesting, but which is quite novel to me. He seems to allocate to the Eastern hemisphere the privilege of being the only place where sprue is found. But I have seen a good many cases of sprue from the West Indies; and most certainly the best clinical description of the disease, and the earliest one so far as I know, was by Hillary, who was a physician in Barbados some 150 years ago. At that time the disease undoubtedly existed extensively in Barbados, and probably in the rest of the West Indies, and I know that it still occurs there. But, although it undoubtedly exists in many parts of the tropical world, it has got a distinct preference for particular parts; I believe there are more cases of sprue in Ceylon, in the Malay Peninsula, in the southern part of China, in the Philippine Islands and the Malay Islands, than in other parts. Still, it does not follow that sprue cannot exist elsewhere.

I should like to know from Dr. Carnegie Brown what is his authority for the statement that the disease originated in the Malay country, and that it has spread thence north and south and west. Has he any authority for saying that the disease existed there before it existed, for example, in Shanghai, or the Philippines, or Ceylon, or India? I have not found any evidence for the truth of such an idea, but possibly he has some.

The predilection of sprue for the European is undoubted, and the explanation of this is not easy to get at. I do not believe that there is such a thing as racial immunity from any disease, so far as man is concerned. I believe that one race is just as susceptible to bacterial or protozoal attack as another. I believe that a negro can get tuberculosis just as well as a white man, and that a white man can get beri-beri just as well as a black man. Any difference there may be is only one of opportunity and circumstance. We know, for example, in the case of dysentery that the Indian is particularly liable to dysentery, and that he gets dysentery more frequently than the European; yet, nevertheless, the Indian is much less liable to liver abscess.

There are certain circumstances which render the European more prone to liver abscess than the Indian; but when the Indian adopts European habits in the matter of eating and drinking he becomes even more liable to liver abscess. So it may be with sprue.

I had a little difficulty in understanding one passage in the Paper, in which Dr. Carnegie Brown seemed to convey the idea that a Dutchman was not a European. He said that, whereas the English supervisor of native labour in the Malay States, although he lived like the Chinese and the natives, was not at all susceptible to beri-beri; yet his Dutch colleague in Sumatra, or elsewhere, was especially susceptible to that disease. Is one to infer from this that the Dutchman has not the pathological qualities of the Englishman?

Dr. Carnegie Brown suggested that sprue was a bacterial disease. Now if he means by this that it depends upon a specific micro-organism, or micro-organisms, I quite agree with him. But if he means that this micro-organism is a bacterium, I am not prepared to go with him. I question whether, considering the geographical limits of sprue, the micro-organism is a bacterium. For if it were, why should you not find the disease in cold climates? Bacteria can live outside the body in cold climates just as well as in hot ones. If the microbe of sprue be a bacterium, then sprue is almost the only bacterial disease that has such a climatic limitation.

As regards the question of auto-intoxication, I am inclined to question whether the symptoms of sprue and dysentery are particularly dependent upon the auto-toxic character of the diseases. I think the symptoms of sprue are dependent upon mal-nutrition rather than on auto-intoxication. I think the principal element that leads to the death of the patient is starvation. If you examine the stools of a case of sprue microscopically, you will find that it is full of fat. If you administer any fatty element in the food of the patient, you will find that it is not digested. You will often find that even milk is passed undigested. The principal general symptoms, therefore, of sprue are, I think, the result of starvation, just as in chronic dysentery, and, in a sense, in cholera.

Dr. Bell: Sprue is extremely rare in Hong Kong, where I have been for twenty years, and of these twenty years I have spent twelve years in hospital. We saw very little of it, and I have never seen the disease in a Chinaman or any other race but a European.

The idea that the disease is an auto-intoxication is a theory which is rather new to me, and I should hesitate to say anything at this moment either for or against it. But I am more inclined to the view that it is purely a disease of nutrition. In the cases which have come beneath my notice, the mouth symptoms, upon which Dr. Carnegie Brown relies to support his theory, have always been the latest to appear: in fact, it is very difficult to diagnose sprue until the patient is very ill indeed. Whether we ought to diagnose it more correctly or not is another matter, but it is very difficult to distinguish between it and chronic forms of diarrhœa. The mouth symptoms have always been late symptoms; and I think, therefore, that my experience does not support the theory of auto-intoxication. If it is a toxæmia, it is a very long and chronic disease.

PROFESSOR SIMPSON: This is not a disease to which I have paid much attention, either from a curative or a preventive point of view; but the cases that have come beneath my notice and the histories which I have gathered incline me to the view of agreeing with Dr. Carnegie Brown, that the cause of this disease is a specific infection. I have noticed cases which seemed to occur simultaneously, and in a manner indicating that food was the medium for the propagation of the disease. I was recently speaking to an Indian officer who had had an attack of sprue; a curious thing about his case was that he came down from one part of India to another part where sprue cases are well known, and he remained there for a week; another friend came from another part, and both were afterwards infected with sprue. Other similar cases have accentuated this impression. However, it is not, as I said, a subject to which I have given very much attention. It seems to me that it is just possible that milk is the medium for the production of sprue in the tropics. It appears also that the preference the European has for milk may in a measure account for this liability. For whatever warnings may be given to the European to drink only boiled milk in the tropics, they are often unattended to. He, perhaps, goes out with the intention of carrying out the warning, and does so for a time, but it is soon forgotten. As you are aware, Sir, in this country you have frequent outbreaks of sore mouth and similar diseases which have been traced to milk infection, that is, milk from animals which have diseased udders. I think, therefore, that it is just possible

that in those countries where you have diseases of cattle, such as rinderpest and its allied forms, that there may be some connection between the two: not between rinderpest, but some disease allied to rinderpest. What gave me that impression was a long series of researches that I made in animals, in the course of which I had to examine a very large number of cattle in India; and I was astonished to find the large numbers which had patches on their mouths and acute intestinal infection, which afterwards became chronic. They had ulcers and many symptoms very similar to those of sprue, My mind was not directed to that subject at the time, and, of course, I did not carry it in that direction at all; but it occurs to me as a suggestion, that in any future research the possibility of some such connection might very well be borne in mind.

As regards immunity in natives, of course I am not in a position to say whether that is a real immunity or not. Those who are in practice will know better than myself. But I must say that I was very much struck the other day when in the Laboratory in the Malay States, looking at some of the specimens which Dr. Fraser, the Director of the Laboratory, showed me, in which he demonstrated that out of a large number of post-mortems he had made, and from which he had prepared microscopical specimens, there was hardly an intestine amongst the natives that was free from ulceration and laceration. This, I believe, is quite a new factor; and we may find that, after all, as Sir Patrick Manson says, sprue may be found amongst natives to a larger extent than is suspected.

DR. LYNCH: I am afraid that I can make no useful contribution to this discussion on sprue. Although Dr. Carnegie Brown states in his Paper that sprue is prevalent in Fiji Islands, where I have practised, I am afraid that I have had no experience of it in those Islands. It has been reported by the chief medical officer that there have been cases of sprue in Fiji, but they must be very rare indeed. Although we have a good deal of chronic dysentery in all its forms, we have, practically, no sprue.

DR. HARFORD: I speak with great diffidence on this subject. I came here to-night because I felt that this is a matter of great practical importance, and I very much hoped to gain some new light on this obscure disease. As physician to a large missionary society, it is becoming a matter of great practical importance to me to know more about this disease. There are several cases in this country

at the present time which we call sprue, which present great difficulties. If I may say so, I am rather disappointed with the Paper put before us to-night. I do not quite see upon what Dr. Carnegie Brown has based his statement. He has given us some account of blood counts, but apart from that he does not seem to have given us any very definite information as to the pathology or symptoms of the disease.

As regards the question of geographical distribution, I think he expressed some doubt as to whether it did occur to any large extent in India. I think there is no doubt that sprue occurs in Bengal, as I have seen at least one case there, and have heard of others. I was examining to-day a series of answers received from a number of medical men in the Punjaub, who are connected with missionary societies: and practically all of them held they had seen no sprue in the Punjaub except as imported cases.

I wish we had heard more to-night as to the treatment of sprue. It seems to me that until we know something more definite as to the pathology of this disease, we must rely more upon the treatment than anything else. I had hoped that Dr. Begg, of Bath, would have been here to-night, as he has advocated the use in sprue of santonin.

DR. MEREDITH RICHARDS: I should be glad if Dr. Carnegie Brown would tell us in what way this disease is spread. Can fresh cases be traced to previous ones, or do they seem to arise without any direct communication with previous cases?

LIEUTENANT-COLONEL MACPHERSON, C.M.G., R.A.M.C.: I have thought, perhaps, that as certain questions have been asked with reference to treatment, I might make a few remarks, since I happen to have suffered from what was considered to be sprue myself. Dr. Finn wrote a Paper at one time in which he described hill diarrhœa as sprue, but I see that Dr. Carnegie Brown has excluded hill diarrhœa from sprue altogether.

I have looked carefully over Dr. Brown's clinical definition of the symptoms of sprue, and I quite agree with Sir P. Manson that we have not as yet had a proper definition of the disease. I confess that I had all the symptoms described excepting stomatitis, which is mentioned as almost invariably present in sprue. I notice that the incubative period is said to be some years, but in my case I had been out to dinner on a cold night, and woke up next morning with

symptoms of hill diarrhœa, which had an onset of twelve hours or so of bilious diarrhœa, followed immediately afterwards by all the symptoms of sprue. I tried all the treatment laid down in the books, but for two or three months I gradually lost flesh and got into a serious state. At the same time I had under my charge a large number of similar cases, which, with the exception of stomatitis, had all the symptoms of sprue, which are here described. They were all young men of soldier age, and therefore below the age described by Dr. Brown. Neither were they of the sex described by him: they were all men. So here we have a certain differentiation as regards age and sex which was very marked in these cases. I had at the same time under my charge certain cases of chronic dysentery, which had similar diarrhœa, but which were totally different in every other way. I should not describe them in any way as sprue, except for the white diarrhœa. But they had nothing of the progressive symptoms of sprue, anæmia, wasting, mal-nutrition, and so on. As regards treatment, I was greatly puzzled. I tried most of the treatment laid down, and I read Sir Joseph Fayrer's work on the subject, but nothing seemed to meet the case thoroughly. There was, however, one constant feature in all the drugs that had been shown to be of use, and that was that they were evidently hepatic stimulants and more or less intestinal antiseptics. None of them had any permanent effect—they cured the case temporarily, but it invariably relapsed. As a result of this, I thought I would try perchloride of mercury. The moment I gave this, the cases improved, even within twenty-four hours; the white fermenting diarrhœa disappeared, and one had normal, bilious, solid stools, but in no case was there relapse. The same treatment was tried elsewhere afterwards; and I have now letters from various parts of India, telling me of medical officers who have tried this treatment, and have found it successful.

I venture to make these remarks because you asked, Sir, if anything was known as to the treatment; and also because I was so much impressed with the resemblance of hill diarrhœa to sprue that I thought this incident might be of interest.

Dr. Carnegie Brown: Mr. President and Gentlemen: first of all, as regards treatment, I may say that personally I think that is, perhaps, the most interesting part of the question—certainly the most important. But one cannot

deal with everything within the limits of a single Paper; and as I was counselled by the Honorary Secretary that it would be advisable to keep to epidemiological aspects as much as possible. I believed, too, that this Society would expect to hear about the geographical distribution and method of extension of this disease, rather than about its pathological bearings, its morbid appearances, and its treatment. But I can only say that it was with much regret that I found myself unable to deal with treatment also.

I would, in the meantime, like to refer to what the last speaker has said about Dr. Thin's description of sprue as hill diarrhœa, and his view that the two diseases are identical. I think, if he will read the book in question again, he will see that that author clearly stated that they were not the same. In this he agrees with all later authorities. Sir Patrick Manson does not regard them as the same; nor, in fact, does any recent writer. I have had little experience of hill diarrhœa, as it occurs in India, but I have seen some very typical cases; I have had large experience of sprue, and I have no doubt but that the two diseases are entirely distinct. There are, however, a good many points of resemblance, the chief of which, perhaps, is that they are both marked by colourless dejecta; in the case of hill diarrhœa, that has been shown to be due to an obstructive catarrhal inflammation of the bile duct; but as to the cause of it in sprue there is much difference of opinion. I am glad, however, that the point has been raised, for these two diseases have been mixed up for a very long time, and much confusion of idea as to the nature of sprue and of hill diarrhœa has resulted. The story is not a new one: it is, indeed, a very old one; and it is not a little curious and interesting to find that, long ago, two graphic and accurate descriptions were published, at a distance of half the world in space and more than a century in time, of the disease we have been considering to-night. The first was in Barbados (as Sir Patrick Manson has corrected me by saying, though Hillary lived and worked in Jamaica also). Hillary described sprue there exactly as we know it now, and no better description of the disease was ever written. He was also familiar with white flux, or hill diarrhœa, and he differentiated them clearly; that is now more than one hundred and fifty years ago. The other description was that of Alexander Grant, a Fellow of the Royal College of Surgeons, of the Bengal Army, who, under the name of hill diarrhœa, described, in 1856, a disease which had been prevalent at Simla and three other adjacent hill stations. It does not

appear that he had seen Hillary's book, or knew of his description. Grant was surgeon to one of the European regiments, which while stationed at Simla had been seriously affected by a peculiar and undescribed disorder, and this, he said, was seen in two or three types. One type, from his description, can be no other than sprue; it is the disease exactly as we know it: and so graphic and accurate is his description, that even if one began the study of his paper with a fixed idea that sprue was impossible in India, and that he was only to have a description of hill diarrhœa, he would have to put it aside, and be forced to confess that if any classification of disease may be made on the basis of its symptoms, this was, indeed, sprue. The second type of cases which he observed was no doubt hill diarrhœa, which is common and prevalent in Simla: his narrative leaves no room for doubt that he saw cases of hill diarrhœa and sprue too; but that instead of seeing two types of one disease he saw two different diseases. Grant said further that this peculiar diarrhœa, which we now think to have been sprue, had never been known in any other hill station than Simla; that it had never been seen at Darjiling, Murree or Naini Tal, and that it was, in fact, confined to three stations, all within 25 miles of Simla. That in itself is sufficient to show that he had something more than hill diarrhœa, which is prevalent at all hill stations, to deal with. There is another peculiar fact: Grant had been in China; he had himself suffered from this disease at Chusan, where he was stationed for three years; and had, I believe, accompanied troops who had served in the first China War back to Simla. I have conjectured that it is possible that the cases of the disease which he described as the first type of hill diarrhœa were in reality genuine instances of sprue occurring in these troops, and that it had been acquired in China; and that at the same time he saw cases of hill diarrhœa which were incidental to Simla, and, owing to the similarity of the symptoms, thought them the same. I know that sprue has been described as an Indian disease; in Sir Joseph Fayrer's "Tropical Diarrhœa" it is described as an Indian disease; but in that book his description of the disorder is not taken from cases that he had seen in India. So far as can be seen, he did not avail himself of his unrivalled experience there, but based his conclusions upon cases that he saw in practice in London; and out of the thirteen cases of which he gives notes it is a remarkable fact that only one who presented symptoms of sprue had

come from India; the others came from China, Java, the Straits and Ceylon, and were, no doubt, typical cases of sprue. I am strongly of the opinion that sprue is a very infrequent disease in India; and I much regret that there is insufficient time to adduce further evidence, if any is needed, of its essential distinction from hill diarrhœa.

With regard to treatment by perchloride of mercury, it is the routine and successful method of treatment of hill diarrhœa, but, after a very considerable experience of it in cases of sprue, it is my opinion that in itself, as a means, or as an aid to cure, it is absolutely useless. The main—and, perhaps, the only—treatment for that disease is dietetic.

I fear that I cannot deal further with this question of treatment to-night, for it is a very large and important one; but, perhaps, on some future occasion, if it can be arranged, we shall have an opportunity of recurring to it.

With reference to Sir Patrick Manson's observations as to the extension of sprue, it is, of course, impossible to bring forward proof that sprue has originated in or near the Malay Peninsula, though there have been many things which lead one to take this view. It is not only the popular view, but there is much fact to support it. Sprue is gradually spreading north; it goes by the routes of trade, and its progress is definite and accurate. It is not known in Japan at all, though it has got to Shanghai, and is extremely prevalent there; yet that port is only two days from Japan, and has identical climatic conditions. Strangely enough, however, it is not very prevalent in Hong Kong. In Ceylon, where it is known as "Ceylon sore mouth," and is exceptionally prevalent, it is popularly believed that it originally came from Java. But these are only theories: and how it is spreading, one way or the other, it is difficult to say. The principal facts are that it is rapidly getting more intense in ports that are in continual communication with each other, and that it is limited to them; that the chief centres of intensity are in the Malay Peninsula and in Cochin China, and that all the ports connected with these places, up to a certain distance, have successively got the infection.

Perhaps I did not make myself sufficiently clear as to the incidence of sprue on non-Europeans, but there is no basis in my observations for the extraordinary inference of Sir Patrick Manson that in my view Dutchmen are not Europeans. As a matter of fact, the Dutch army in Java is not largely a native one; unlike our

Indian army, it is not native at all; but there are serving in the Dutch army and navy in the Netherlands Indies a very large number of men born in Java of Javanese mothers. I instance that as being one reason why their troops might be expected to suffer less from a disease that is almost peculiar to people who are of actual European birth.

As to race predilection, I, of course, attach much weight to Sir Patrick Manson's great authority that negroes are just as *liable* to get the same diseases as white men; but, as a matter of fact in my own experience, Chinese and Indians and Malays do not do so. If there is one thing that is notable about tropical diseases, it is predilection in the different races to different diseases.

Dr. Bell says he has seen mouth lesions only as a late symptom: I should say that that is very exceptional. My own experience of sprue is that the mouth is prominently affected first in 80 per cent. of all cases, and that the lesions are present sometimes ten years before the diarrhœa comes on. In the same proportion of cases, they persist intermittently during the course of the disease, and in the final stages, when exhaustion and toxæmia are marked, they are always characteristic and severe. Preliminary mouth symptoms are perhaps even more frequent than my estimate; and if in the examination of a case it were stated as an assured fact that there were no mouth lesions at any time, I should have great suspicion as to whether the disease in question was really sprue.

REAL AND APPARENT DIFFERENCES IN THE INCIDENCE OF CANCER.[1]

By E. F. BASHFORD, M.D., General Superintendent of the Imperial Cancer Research Fund.

(*Read: Friday, January* 18*th*, 1907.)

THE separation of the real from the apparent differences in the incidence of cancer is the immediate goal of the statistical study of malignant new growths. The separation is difficult to effect. In attempting to distinguish some apparent differences, and to emphasise others which appear to me to be real, I shall have to crave your indulgence. It will be necessary to discuss many topics not obviously associated, and to endeavour to unravel a mass of detailed observations. Within the short space at my disposal, I shall require to be as dogmatic as possible, in order to bring out the differences which seem to be of real importance at the present time.

At the outset, therefore, I wish to guard myself against the imputation that I attach no importance whatsoever to many of the differences I shall describe as more apparent than real. I shall assign them to these respective categories with reference to their direct bearing upon experiment, in the present state of our knowledge.

The study of all the circumstances associated with the sporadic occurrence of cancer must remain indispensable so long as we are unable to test the relative importance of each. The relative importance of some of these circumstances can only be finally cleared up after the true nature of cancer has been ascertained, and the purely statistical investigation of the incidence of cancer will remain more or less empirical until this end is attained. The statistical investigation of infective diseases was pursued empirically before the developments of bacteriology directly demonstrated the causes of many of those diseases, and placed new problems before statisticians, who were enabled by those developments to see old problems in their true perspective, *e.g.*, the geographical distribution of infective

[1] The term "cancer" is used throughout for convenience to designate malignant new growths of all descriptions.

diseases, their epidemic and endemic occurrence, the relation between variations in the incidence of infective diseases, and, *e.g.*, water supply, density of population, rainfall, ground-water, or season. In the case of cancer, the statistical investigator has not yet advanced from the state of ignorance in which the student of the infective diseases compiled statistics in the days before Pasteur, and it would be unjust to criticise the uses accurate statisticians make of the available data.

Until we shall be able to start cancerous proliferation in a tissue at will, we shall remain in this same unfavourable position for determining the true importance of many circumstances, which at the same time it is unjustifiable to ignore. The increased number of deaths recorded from cancer, its apparent greater frequency in some geographical areas (whether large or small) than others, the presumable importance of race, diet, soil, climate, are all problems of much less importance than the infective or non-infective nature of cancer; but we must not lose sight of the fact that it is in all probability as much without the province of statistics to supply the direct answer to the question, What is the cause of cancer? as it was for statistics to directly prove the causes of diseases now known to depend on infective organisms.

Much harm has resulted from the improper use of statistics by those too enthusiastic advocates of this or that speculation on the nature of cancer, who have ignored the limitations to statistical investigations. Accurate statistics of all the circumstances associated with the sporadic appearance of cancer have their proper place. They are at present the best guide in defining the direction experimental investigation into the nature of cancer should take.

Statistics must be based on accurate data of a nature fitted to the end in view. In the case of cancer, there is a peculiar difficulty in securing accuracy in the data. There is lack of uniformity in the method of compiling existing statistics.

In a general survey of statistics on the incidence of cancer, variations in its recorded frequency are the outstanding feature. These variations have attracted much attention, but there is no unanimity as to the conclusions to be drawn from them.

Cancer is more frequently recorded in some countries and races of mankind than in others. Its recorded frequency varies in the same country, and in urban and rural districts at different times; and in more limited areas, *e.g.*,

in streets and houses, importance has even been attached to the larger number of cases of cancer treated in hospitals nowadays. As is well known, the frequency of cancer increases with advancing years, and it attacks the several organs of the body with varying frequency. The belief was at one time general that the disease was peculiar to mankind, but cancer is now known to occur throughout vertebrate animals. Here again its appearance presents irregularities, in that it is more common in domesticated animals than in wild animals, and more frequent in some domesticated animals than in others. A scrutiny of the nature of the data on which statements of this varying incidence are based is a necessary preliminary in order to arrive at provisional conclusions on the importance of each of the above-mentioned variations. Above all, it is essential to determine if any variable bears directly on the remaining variations, diminishing or augmenting their magnitude, or absolutely changing their significance.

Difficulty of Recognising Cancer.

The pathological value of the data on which statistics of cancer are based is of prime importance. In the exanthemata and other infective diseases, the fully-developed disease, once it has been recognised as a clinical entity, presents itself in the mortality returns as a magnitude which can be compared from year to year, for there is a definite something to be recognised and recorded. Thus, for example, diphtheria, in addition to larval and ambulatory forms, occurs as a well-marked clinical entity in the majority of cases; so that its recognition nowadays presents fairly constant difficulties, and its relation to the general death-rate can be compared from year to year. The same may be said of tubercle, diabetes, and exophthalmic goitre. In cancer, on the contrary, we have to deal with the difficulty that the fully-developed disease, progressing to a fatal issue, may be entirely overlooked by the most competent observer, and not in a small proportion of cases, but even in so high a proportion as 50 per cent., *e.g.*, in the fatal internal cancers. Hence the records of deaths and estimates of mortality, from cancer from clinical data alone, may vary within wide limits, the absolute incidence of the disease remaining, however, the same.

In order to obtain an estimate of the range of these limits, an attempt has been made to correlate the most reliable form of clinical diagnosis with the results of skilled

pathological examination in every case. This was achieved by the collaboration of members of the staffs of the large London hospitals, providing succinct records of the cases, of cancer in their practice, as well as of those cases which, although regarded clinically as malignant disease, were found on pathological examination not to be so. Thus the diagnosis of cancer was confirmed by pathological investigation in 3576 cases; 319 cases similarly diagnosed were found not to be malignant new growths at all, or nearly 10 per cent.; 726, or 16 per cent. of the cases in which diagnosis other than that of malignant new growth had been made, were discovered on pathological examination to be malignant new growths.

The importance of these figures for all statistical investigations of cancer is clearly manifest when the proportions of cases not diagnosed, and wrongly diagnosed, are studied according to the sites of the body in which the disease had originated. Those parts of the body easily accessible to complete physical examination are contrasted in the accompanying Table with inaccessible sites, and with sites intermediate between the two.

LONDON HOSPITALS.

Analysis of Cases Reported by the Hospital Authorities.

—	Malignant New Growths.		
	Correctly Diagnosed.	Not Diagnosed.	Wrongly Diagnosed as Cancer.
Accessible	2391	218	190
Inaccessible	614	420	68
Intermediate	571	88	61
—	3576	726	319

The result appears conclusive as to the factor determining the accurate recognition of malignant new growths in hospitals. More than half of the cases not diagnosed (420 in 726) occur in inaccessible sites. While less than 10 per cent. of the malignant new growths in accessible sites are not diagnosed, more than 40 per cent. of those in inaccessible situations are clinically unrecognisable as cancer.

The pathological process is the same in all the different sites of the body. The great difficulty of diagnosing malignant new growths in internal organs is due to the

fortuitous and occasional character of the symptoms on which the diagnoses are based. Surgeons are more and more recognising that cachexia, pain, and other reputed symptoms are inconstant accompaniments of malignant new growths. Wilks[1] pointed out emphatically, forty years ago, as the result of experience gained in the performance of 2000 autopsies at Guy's Hospital, "the cachetic condition spoken of in cancer is a result of the disease, and does not pre-exist, and in very many cases is not present at all, and depends, as we have before remarked, upon accidental circumstances." The experimental study of cancer in animals fully justifies the conclusion Sir Samuel Wilks—the *doyen* of English pathology—came to so long ago. The survival to the present day of this phantom symptom of cancer is but one illustration of the impossibility of setting up any better substitute or any series of signs as the characteristic symptoms of the disease. This impossibility, revealed by the figures quoted above, needs only one other illustration. Distinguished surgeons have confessed that they could not always be sure of the nature of certain morbid growths. They have got out of the difficulty by designating a group of conditions as pre-cancerous, because, although not conforming to the empirical symptomatology of cancer, cancer as a matter of fact frequently followed. To take the case of the tongue: here this state of affairs persisted till, with the valuable collaboration of Mr. Butlin, whose experience of such conditions of the tongue is perhaps unrivalled, Murray and myself were able to show that four out of seven lesions which Mr. Butlin believed to be pre-cancerous conditions of the tongue were in reality already well-developed, if small, epitheliomata and clinically unrecognisable as such. Here, in a site accessible to the most careful physical examination, the difficulty of diagnosis is clearly brought out. At the same time the probability of correct diagnosis is shown to depend not on symptoms, but on the size to which a cancer, a purely anatomical lesion, must attain before its character is recognisable to the unaided senses, or even with the assistance of the microscope.

The extent to which the difficulties of diagnosis tend to conceal the absolute incidence of cancer varies at different age-periods. The difficulties are more pronounced in children, for in them investigation is entirely objective, and the absence of features which are specific for cancer is most

[1] *Guy's Hospital Reports*, S. III, vol. iv, 1868.

felt. A comparison of the percentage relationship of the distribution of malignant new growths (on the basis of the figures already quoted) at ages below 25, which were not diagnosed, and of those growths which had been wrongly diagnosed as cancer, brings out the fact that a much higher proportion of cases of malignant new growth cannot be recognised clinically in youthful patients. When the cases are grouped under ten instead of under twenty-five years, a still greater discrepancy is revealed.[1]

We have no means at present of estimating the extent to which the figures of the cancer-mortality of the general population would be modified, were it possible to determine the disturbance introduced by cases wrongly diagnosed as cancer, and not diagnosed respectively. This difficulty is augmented by the fact that the figures, on which the estimate of the proportion of cases wrongly diagnosed as cancer is based, are derived from operation cases; while the estimate of the proportion of malignant new growths which were not recognised is based to a greater extent on post-mortem material, which compares much more strictly with mortality returns. In the national mortality returns the mode of death helps to decide whether the lethal issue was due to cancer or not.

It might seem that the errors in the final data, arising from the occurrence of growths wrongly diagnosed as cancer, will neutralise the under-estimate caused by cases which have not been diagnosed; but a little consideration shows that this is not the case. The under-estimate of the frequency of cancer is not uniform at all sites, and the sites where the under-estimate is greatest (internal organs) are not characterised by a corresponding over-estimate as the result of wrong diagnosis of cancer.

These considerations show that the errors in the one group cannot be set off against the opposite errors in the other group, in such a way that the final totals should represent the absolute incidence of the disease in any organ or in the body generally.

It is impossible to apply any correction from hospital statistics to general mortality statistics. It is therefore fallacious to make any direct comparison between the death-rates from cancer in the general population and the proportion of cases occurring in the patients of a hospital or group of hospitals, although the clinical observations which constitute the starting-point of both forms of statistics are

[1] Bashford and Murray, *The Statistical Investigation of Cancer, Sec. Sci. Rep. of Imp. Canc. Res. Fund* (Taylor and Francis, 1905).

similar. The death-rate of a population is the most—and probably the only—reliable method of estimating the frequency of cancer. All other methods, such as the German "cancer-census," the study of the frequency in the experience of life-assurance societies, the comparison of the numbers of cases in hospital practice in which no basis for comparison exists, introduce either new sources of fallacy, or magnify those inherent in mortality statistics. The errors in diagnosis made in general practice are probably greater than in hospital practice, for they are made under less favourable circumstances.

In endeavouring to estimate the importance of the variations in the incidence of cancer, I shall attach great importance to the very wide limits within which the primary data may vary qualitatively and quantitatively under different circumstances.

Apparent Differences in the Recorded Incidence of Cancer in Europe.

There are differences in the number of deaths assigned to cancer in civilised countries. Owing to their exceptional characters, I do not propose to touch upon the statistics of the United States or of the Australasian Colonies. In Europe, *e.g.*, the rate of mortality varies from 0.33 in Hungary to 1.26 in Switzerland. It may not be only a coincidence that the largest number of deaths assigned to cancer occurs in Switzerland[1], where medical inspection of the dead body is customary, and where in 1900 in 15 of the largest towns autopsies were made in so high a proportion as 25.7 per cent. of the total deaths. I cannot refrain from pointing out that the number of deaths assigned to cancer increases from one country to another in a manner parallel with the increasing accuracy of the vital statistics of the several countries. Thus, for example, the Prussian statistics are known to be less reliable than those compiled by Dr. Tatham for England and Wales, and the rate of mortality from cancer is 0.57 as compared with 0.79. The recorded death-rate from cancer in Ireland is much smaller than in the rest of the United Kingdom, being 0.57, equal to that of Prussia; and I may take this difference as a special test case, because a possible explanation has been arrived at for Ireland.

The discrepancy between the recorded incidence of

[1] Cf., however, p. 51 for factors artificially augmenting the number of deaths from cancer.

cancer in England and Wales, and Ireland, exists also in the extent to which cancer is recorded in the hospitals of the two countries.[1] The fact has been elicited that autopsies are performed with minimal frequency in Irish hospitals,[2] whereas in English hospitals they add largely to the certified number of deaths from cancer. Further, in Ireland microscopical examination is scarcely carried out at all, outside of one or two centres of population; and in England, together with the number of autopsies, is responsible for adding over 30 per cent. to the total number of cases recorded in hospital.

A general review of the facts elicited on the diagnosis of cancer in London and Irish hospitals reveals the magnitude of the differences which may exist between the recorded frequency of cancer and its absolute incidence. Procedures, which in London and England generally make the recorded frequency approximate more nearly to the absolute incidence, are inoperative in Ireland. The discrepancy between the recorded frequency of cancer in London and Irish hospitals can be explained solely by the heavy disadvantage under which the search for cancer is carried out in the latter. The very unsatisfactory circumstances under which a large proportion of medical practitioners have to eke out an existence in Ireland is notorious, and finds its counterpart in the registration of the causes of death.

The conclusion is permissible that among that proportion of the Irish population which does not have access to hospitals, a still higher percentage of cases of cancer remains unrecorded; with the result that the relative frequency in hospital and the relative infrequency outside of hospitals, together combine to give a lesser-recorded cancer mortality throughout Ireland generally. In all probability, the more favourable conditions prevailing in England, if they existed in Ireland, would quickly demonstrate there a cancer death-rate proportionately higher than that of England, in accordance with the higher "age-constitution" of the Irish population.

The occurrence of cancer in Ireland has been made the subject of a special report by the Registrar-General for Ireland,[3] the perusal of which only confirms the unfavour-

[1] Cf. Bashford and Murray, *The Statistical Investigation of Cancer.*

[2] Not only are the facilities for *post-mortem* examination lacking, but the habit of holding "wakes" on the dead is a great obstacle in the way of obtaining permission for autopsies.

[3] "Special Report on Cancer in Ireland," Supplement to *Thirty-Eighth Annual Report of the Registrar-General* (Dublin, 1903).

able opinion I have above expressed on the insufficiency and unreliability of the data upon which the Registrar-General of Ireland is obliged to rely for his statistics of cancer mortality; and also arouses misgivings as to the extent to which it has been found possible to apply actuarial corrections for the peculiar age-incidence of cancer.

Throughout Europe such disturbing factors are in play, minimising the number of the data available for statistical purposes in some instances, and augmenting them in others. The pathological value of the data is also by no means uniform. If one be justified in dismissing the difference between the rate of mortality in Ireland, and England and Wales, as an expression of an apparent and not of a real difference in the absolute incidence of cancer, the differences obtaining in the case of other European countries cannot have any greater importance attached to them. The primary data are obtained in different ways, and different statistical methods are employed in different countries. Therefore great caution is necessary in assuming that the final statistical results are comparable, and reveal real differences. In any case, the magnitude of the recorded differences loses much in significance. In some statistics, the attempt is made to deal separately with the deaths from sarcomata and carcinomata. This probably introduces grave errors, for Murray and myself have shown that the one form of disease is as difficult to recognise clinically as the other, and also that the probability is great that carcinoma and sarcoma both increase with advancing years: a conclusion to which Weinberg has come independently. In other statistics, new growths are grouped together, in a more indiscriminate fashion, *e.g.*, in Switzerland, for males, all fatal diseases of the prostate gland are grouped under the heading of "cancer" of that organ. The factor introducing most disturbance into the number and the value of the data is probably the manner in which the certification of deaths is effected, and the extent to which this is solely the duty of medical men, as in some States, or merely the ignorant opinion of a layman, after viewing the body, in others. Prinzing cites two instructive cases. In one, an ignorant peasant who performed this duty returned all deaths as due to cardiac failure, and another returned fifty deaths from diphtheria in Tilsit, at a time when even illness from diphtheria was quite rare.

The improvements Drs. Ogle and Tatham have effected in our own national statistics of cancer, by inquiring into vague statements of the cause of death, of itself serves to

show how much room there is for improvement in countries where laymen are entrusted with the declaration of the cause of death in the case of cancer—a disease often presenting insuperable difficulties to the most skilled clinician, as I have pointed out above with reference to hospitals.

Before the members of this Society it is unnecessary for me to emphasise that the statistical utilisation of the number of deaths recorded from cancer requires the employment of special methods, because of the frequency of the disease in old people and its rarity in the young. This fact has not received so much attention abroad as in England, where Newsholme has so ably enforced its statistical importance. I am obliged to draw attention to the frequency with which statistics on cancer have been compiled without any cognisance being taken (1) of the pathological value of the data; (2) of the actuarial corrections for the error due to the survival of a varying number of persons to higher ages; (3) of the futility of conclusions based on too small numbers, *e.g.*, in small districts. These are sources of fallacy any one of which may completely vitiate comparisons, and which, I regret to say, are not always absent from the reports of medical officers of health in this country, who occasionally alarm their neighbourhood by, *e.g.*, permitting such statements as, "There was a considerable increase last year in the number of deaths from cancer, and also from whooping-cough and suicide."

In briefly summarising the impression made by a study of the death-rates from cancer in European countries, I may state that comparisons between different countries, with a view to establishing differences in the absolute incidence of cancer, appear to me to be entirely fallacious. The dimensions of the differences are not so great that they are incapable of explanation by (1) the varying difficulties in the way of obtaining accurate records of the numbers of deaths from the disease, *i.e.*, of making them approximate to the absolute number; (2) the divergences in the methods of utilising the data for statistics; (3) the varying extent to which actuarial correction is made for the age-constitutions of the respective populations; (4) the different age-constitutions of the populations themselves. I must guard myself from the charge that I deny real differences may exist. All I intend to convey is that the recognisable sources of fallacy appear to me to carry more weight than the evidence that the existing differences are real, and of sufficient magnitude to make them of primordial importance for the experimental investigation of the nature of

cancer. As regards more limited areas in single countries, and differences between towns and country districts, the accuracy of the registration of the causes of death is everywhere behindhand in rural districts as compared with towns; and the same remarks appear to be applicable here as to the differences which obtain in the rate of mortality from cancer in more extended areas.

Apparent Differences in the Incidence of Cancer outside Europe.

When attention is directed to races of mankind outside of Europe, including aboriginal races, the differences in the recorded incidence of cancer are of greater magnitude. These differences are chiefly relied on by those who assert that our European civilisation is casually connected with the recorded increase in the number of deaths from cancer.

The case of Japan is of special interest. In 1901, the German Cancer Committee seriously accepted information to the effect that cancer was, without doubt, much rarer in Japan than in Europe. The informant went on to state: "This is at once evident from the relatively large number of cases in the small number of European inhabitants, as contrasted with the rarity with which the disease is observed in natives."[1] Without referring to the statistical fallacies which vitiate such a conclusion, it is sufficient to point out that, as a matter of fact, the official statistics of the Japanese Empire for that same year show that out of a total of 959,126 deaths, 24,598 were returned as due to "cancer" and "other malignant growths."[2]

I have to thank Baron Takaki for access to the Japanese statistics. He expressed the opinion that cancer was not so well diagnosed in Japan as in England, nor were the mortality statistics of Japan as yet comparable in accuracy to those of this country. The approximation of the Japanese to the English national figures is thus made all the more striking. The crude figures would indicate that cancer is twice as frequent as a cause of death in England as in Japan. It must be evident, without further discussion, that this conclusion might require drastic revision if our information as to the "age-constitution" of the Japanese population were more complete, and if the registration of

[1] *Verhandl. d. Comites f. Krebsforsch*, Heft. 1, p. 46.

[2] In England and Wales in 1904, out of 549,784 deaths, 29,682 were returned as due to cancer. The population in 1904 was calculated to be 33,861,210. The population of Japan in 1901 was 45,227,464.

deaths were carried out as in this country. In Japan, in 1901, no fewer than 52,786 deaths were recorded as due to old age, and 113,474 as due to undefined diseases.

Exaggerated importance, not justified by fuller knowledge, has been attached to assertions that cancer is practically absent in India, in Egypt, and among aboriginal races.

In the course of the past two years 1288 cases have been reported from hospitals in India. Considering the 200,000,000 of population this number seems vanishingly small, but must be regarded in the light of the small number of hospitals, and the onerous duties which a relatively small number of officials, undertaking this additional work, have to discharge. More than 90 per cent. of the cases are recorded for sites very accessible to physical examination. The patients belong to vegetarian as well as other castes, and their distribution throughout India suffices to dispel any hopes of discovering races exempt from the disease in that country. The rarity in the records of cases from internal organs does not necessarily imply that such cases do not occur. The difficulty of diagnosing internal cancer has already been referred to as of statistical importance; and these difficulties must be much greater in circumstances such as are met with in India, and to a still higher degree in less civilised countries. In the case of Egypt, among the patients treated in the Government Hospitals, 193 cases of cancer have been reported during the past two years. In short, wherever there is a well organised medical service controlling hospitals in outlying parts of the empire, reports of the occurrence of cancer have been obtained, with certain exceptions where the smallness of the populations has precluded its occurrence up to date. The relative ease with which reports have been obtained through the instrumentality of the Colonial Office contrasts favourably with the difficulties to be overcome in obtaining them.

I do not propose to discuss in detail the observations which have accumulated since the commencement of our inquiries, as to the occurrence of cancer in the native races in outlying parts of the British Empire and remote from civilisation. It will suffice to point out that the disease has been found where formerly it was supposed to be absent, but the figures are still too small to merit detailed consideration. The facts ascertained show that, taking England as a standard, there is a gradual diminution in

the precision and completeness with which cancer is recorded, Ireland showing less precision and completeness, and various outlying parts of the empire still less of these qualities, till a minimum is reached among the natives of certain tropical colonies, and in the case of islands with very small populations. The diminution proceeds *pari passu* with the increasing difficulties in observing the disease, or obtaining reliable primary statistical data of any sort whatsoever. These considerations modify the importance to be attached to differences in the recorded incidence of cancer in Japan, India, Egypt, and uncivilised races, for they are paralleled in Europe if in lesser degree.

It may be opportune to remark here that although cancer is universal, it is everywhere a rare disease. Even in countries in which it is a relatively important cause of death, the number of cases is small in comparison with the total population. The differences in European countries only amount to fractional parts of 1 death per 1000 living. The data which would enable us to compare Central African with European races in the same way are totally wanting.

Reviewing the incidence as a whole, the balance of probability is in favour of the view that the recorded differences in the frequency of cancer in European and other races are more apparent than real. They are therefore unlikely to afford safe guidance to experimental investigations, or to throw direct light on the truth of the assumption they have so frequently been used to support, viz., that cancer is a disease, of which the several cases occurring in a population are causally connected by a common virus passed from one person, directly or indirectly, to another. I do not underrate the value of the statistical investigations above described, when I assert that their continuance does not promise to yield data numerous and reliable enough to reveal the real differences which may exist within a measurable time. Data bearing only on the ethnological distribution of the disease require to be supplemented by other investigations when we attempt to draw conclusions forthwith.

Comparative Biological Importance of the Age-Incidence of Cancer.

Throughout the ethnological distribution of cancer, one fact is constant and prominent. The maxima in the number of cases recorded always refer to later adult life or

advanced age. Progressive diminution in the recorded frequency of cancer, as described above, for the *genus homo* presents itself when consideration is turned to other representatives of the vertebrate phylum, and the frequency of cancer in domesticated and in wild animals is compared. If it be unjustifiable to directly compare the data on the incidence of cancer in different races of mankind, it is still less justifiable to compare the incidence of cancer in one class of the vertebrates with its incidence in others. Nevertheless, the data exhibit features which have important bearings upon the nature of cancer in man, even in the absence of valid statistical comparisons. In a series of Papers, the importance has been emphasised of the occurrence of cancer in domesticated and in wild animals, and I must refer to them for details.

Investigation has proved that cancer occurs in mammals, tame and wild; in birds, tame and wild; in amphibia, in fresh-water and in marine fish, and its occurrence in the latter when living in a state of nature possesses no little interest The only class of the vertebrates in which the disease has not been described is the reptiles, in whom, however, benign new growths are known to occur. In the case of some domesticated animals, *e.g.*, mice and cattle, the systematic examination of large numbers of animals has already shown that the frequency of the disease in them varies from one case in 1500 to one case in 3500, approximating therefore to the frequency of the disease in a population of all ages. Attention has only recently been directed to this matter. The data already obtained, however, appear to indicate that when the full facts are known, the frequency of cancer, at any rate in some domesticated mammals, will approximate very closely to that of civilised man. The most important result of this line of investigation is the establishment of the fact that the peculiar age-incidence of cancer in man is a law certainly for all the domesticated mammals. In the sparser data from other vertebrates, there is no evidence against its wider application; but, on the contrary, much that supports the view that cancer develops in constant relation to the absolute duration of life, whether it be long or short. At every step one has been met by the fact that the ease with which cancer was discovered stood in direct relation to the number of aged animals examined, and to the extent of the facilities for making observations on them.

While new growths are less frequent in animals than in man, a consideration of the causes of this infrequency

serves only to emphasise the importance of old age in determining their occurrence. The relative infrequency with which new growths are recorded in animals other than man is probably due to various causes. Where the tenure of life is short, the period of comparative immunity from cancer is correspondingly shortened, but the period of maximum liability is still more greatly abbreviated; *e.g.*, in the case of the mouse, these periods are respectively two years and one year. In cases in which life is much longer than in man, *e.g.*, in many of the reptilia, where the duration of life is reckoned sometimes by hundreds of years, the total numbers of animals coming under observation at the time when they are most liable to cancer is extremely small. In the case of wild animals, those approaching decrepitude are either killed off or die of starvation. Under their natural conditions of life, animals rarely survive the period of functional activity of the reproductive organs. The cogency of these observations is reinforced by the relatively greater frequency with which cancer occurs in the domesticated mammals, and more particularly in those which, for sentimental or commercial reasons, are allowed to attain old age in relatively greater numbers, *e.g.*, in the horse, the dog, the cat, and old female cattle, where the latter are allowed to attain almost the absolute limit of life when peasants keep them for draught purposes, or for breeding. On the contrary, among those domesticated animals which are killed off when still young, so soon as they have become marketable commodities, *e.g.*, pigs, cancer is extremely rare. The frequency of cancer among the negroes of America contrasts with the difficulties encountered in searching for the disease among the natives in Central Africa; but it also adds force to the same line of argument. All the preceding considerations lead one to suspect that civilised man's responsibility for the occurrence of cancer among native races brought into contact with civilisation, and in domesticated mammals, may merely be limited to providing them with opportunities for reaching their respective cancer ages.

The comparative biological study of cancer has given new significance to the difference in the incidence of the disease in young and adult individuals. It is a real difference, and of fundamental importance in elucidating the nature of the disease. Accurate statisticians have long given careful attention to its statistical importance; and although it has been the stumbling-block of most hypotheses, pathologists in the past have not accorded it the importance it now deserves in the light of recent research.

The increasing frequency of malignant new growths as age advances in domesticated animals, and their restriction to advanced age in those animals in which only isolated cases have been observed, gives a totally different aspect to the age-incidence of cancer in man, the species in which our knowledge is most complete.

It has, indeed, been asserted repeatedly in Germany that cancer is becoming more frequent in young people than it was, and that the alleged increase of cancer is due partly to this phenomenon. The allegation of this departure from a biological law of such wide application as the age-incidence of cancer at once demands attention. The national mortality returns do not support this view for England and Wales, the increase in the recorded number of deaths being greater for the higher-age periods. As regards German statistics themselves, the figures for the town of Berlin indeed show exactly the opposite, a much greater apparent increase in higher ages. With reference to the Prussian statistics, Weinberg remarks: "In Prussia especially, mortality statistics have markedly improved, in so far as many towns have introduced death-certification by medical men, and in addition the populations of the towns have increased relatively and absolutely, side by side with the more accurate statistics pertaining to them. It is therefore not to be wondered at that Wutzdorff has recorded an increased frequency of cancer in the younger age-groups."[1]

In asserting the fundamental importance of the increasing frequency of cancer with advancing years, one is at once confronted with the fact that cancer is not absent from early life,[2] but on the contrary occurs in measurable amount from birth onwards. The fact does not detract from the importance of its predominating association with senescence, for the organs attacked in the young acquire added interest, when once it is realised that the association of cancer with senescence may be of importance in framing conceptions of the nature of cancer, its conditions of origin, and the relations of cancerous proliferation to the growth of the individual.

[1] *Münch. Med. Woch.*, No. 50, 1905.

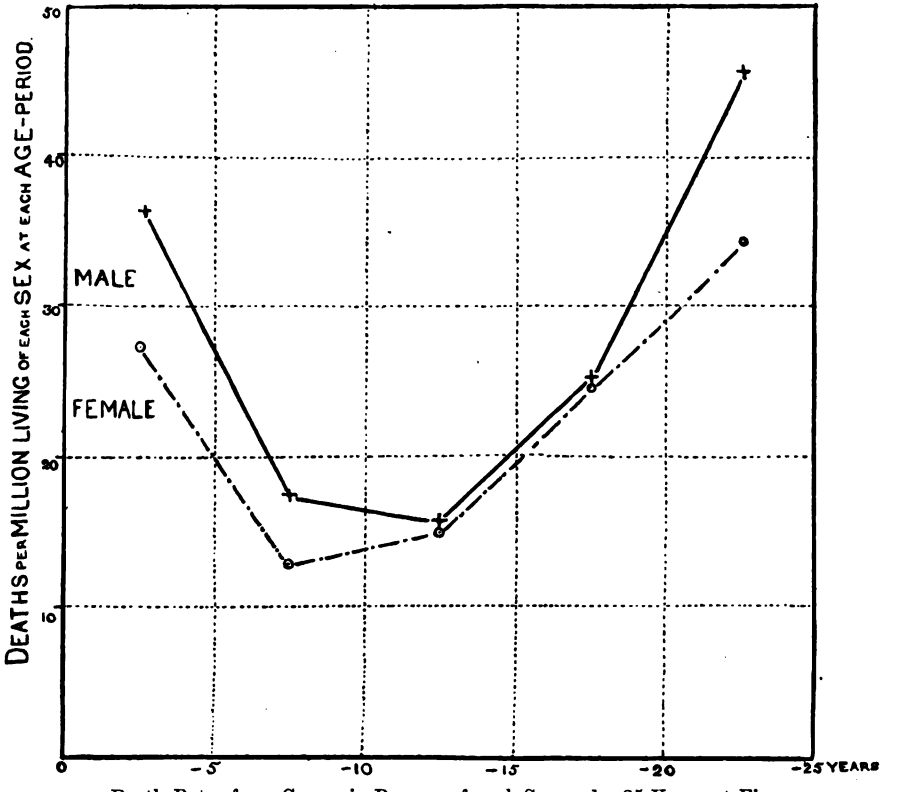
[2] In the same way a certain proportion of individuals reach extreme old age (90 years and over) without developing malignant new growths. Whether in these cases the period of liability has passed, and a condition attained comparable to the minimum in early life described below, or these aged people escape because of the absolute rarity of cancer even in the aged, cannot be determined at present with the data at my disposal.

The organ-incidence of cancer in children is apparently widely different from that which in later life makes up the great mass of fatal cases. Tumours of congenital origin —often of complicated structure—form a considerable proportion. Growths in the neighbourhood of the kidney, many of which probably fall into the same category, are also present in a considerable proportion of children dying of malignant disease. Sarcomata in various regions of the body, but especially in connection with the bones and the central nervous system, form a large contingent. The structures which in later life are especially prone to cancerous transformation are at this time almost entirely exempt. The years immediately following birth may be considered as a period of senescence of many fœtal structures whose function has been fulfilled, and probably of many other formations which, although never exercising any function, and regarded as abnormalities and deformities, are yet merely pathological aberrations of structures normally present in man, or in lower animals. That many of the cancers met with in the earilest years of life may be special manifestations of the age-incidence of the disease is made possible by a peculiarity in the incidence of cancer in early years. When the death-rates from cancer in the general population of England and Wales at different age-periods are compared, the death-rate progressively diminishes as younger age-periods come under review. When the deaths from cancer of persons under twenty-five are stated as death-rates per million living at intervals of five years, it is found that the diminution does not extend uniformly back till birth. On the contrary, a minimum is reached between the fifth and fifteenth years. The mortality among females is also noticeably less than in males, in contrast to what obtains in later life. In the crude figures from hospitals the same features are present. This diminution in the cancer death-rate is sufficiently important to deserve attention. The statistics of mortality for Berlin, for Prussia, and for Bavaria exhibit the same minimum—also lower in females. It is the only minimum which the collective death-rate from cancer shows after birth, and appears to be an expression of a real difference in the incidence of the disease.

We can thus infer that it will be possible to attain to a further insight into the incidence of cancer when an analysis is made, not with reference to individuals, but with reference to the organs composing the body. The increase is not uniformly progressive and simultaneous for

all organs. The span of life of the individual is not the same as that of the separate organs and tissues contributing to its maintenance. The varying age-incidence of cancer in different organs of individuals of the human race presents contrasts similar to those found in different animals with long and short lives.

Cancer of the stomach becomes frequent earlier than



Death-Rates from Cancer in Persons of each Sex under 25 Years, at Five Age-Periods. Average for 1901. England and Wales.

cancer of the skin, cancer of the uterus and mamma are more frequent towards the decline of reproductive activity than in the earlier years of life; and, to take an extreme case, cancer of the chorion follows closely upon the period when this tissue, having fulfilled its transitory function, begins to undergo involution.[1]

[1] For this reason ordinary chorion-epithelioma occurs fairly uniformly throughout the period of reproductive activity. The period of its greatest

Looked at biologically, chorion-epithelioma presents a perfect parallel in man to the incidence of cancer in short-lived animals.

Regarded from this standpoint, the age at which cancer is at a maximum in a population depends upon the ageing of the tissues in which it takes origin, much more than on the absolute ages of the individuals in whom it occurs. The sharp contrast prominent between long- and short-lived animals respectively is obscured for the organs of individuals. Just as two years old in one species of animal may correspond to sixty years old in another, so relatively wide limits obtain in the period within which the same tissues in different individuals enter upon their period of senescence. The future combination of statistical and other forms of study must determine whether anything comparable with the fall described for childhood occurs for individual tissues, *i.e.*, whether the individual tissues having passed a stage at which a maximum incidence is reached, the danger tends to diminish. The data at present available appear to indicate a progressive advance for some tissues, and a rise followed by a fall for other organs; but no definite conclusions may yet be drawn.[1]

In the preceding pages I have attempted to show that the variations in the incidence of cancer in civilised peoples are not great, and are probably apparent. The nature of the evidence available with reference to the occurrence of cancer in uncivilised peoples and savage races has been reviewed. Here also the prominent differences obscure those that may be real.

All the obvious differences together have less value for investigation than one phenomenon which is of practically universal occurrence. The differences due to the relative proportion of aged individuals in a population, whether human or animal, are more constant and therefore real. They call urgently for explanation, and must engage the energies of those carrying on the study of cancer until solved. They are paralleled by the differences between the frequency of cancer in different organs of the human body in the English national statistics. They are directly accessible to statistical study, are real, and their accurate investigation has a direct bearing on the nature and

frequency must be considered biologically with reference to the generation of which it forms a part, viz., the fœtus and not the mother. It is, however, impossible to obtain this separation for statistical purposes.

[1] Many *aged* people escape the risk of cancer; cf. the remarks in footnote on p. 58.

ENGLAND AND WALES.

Deaths per 1,000,000 *Living at each of the Age-Periods given. Average* 1901 *to* 1904, *illustrating the Different Age-Periods at which Cancer of Certain Organs begins to increase rapidly in frequency.*

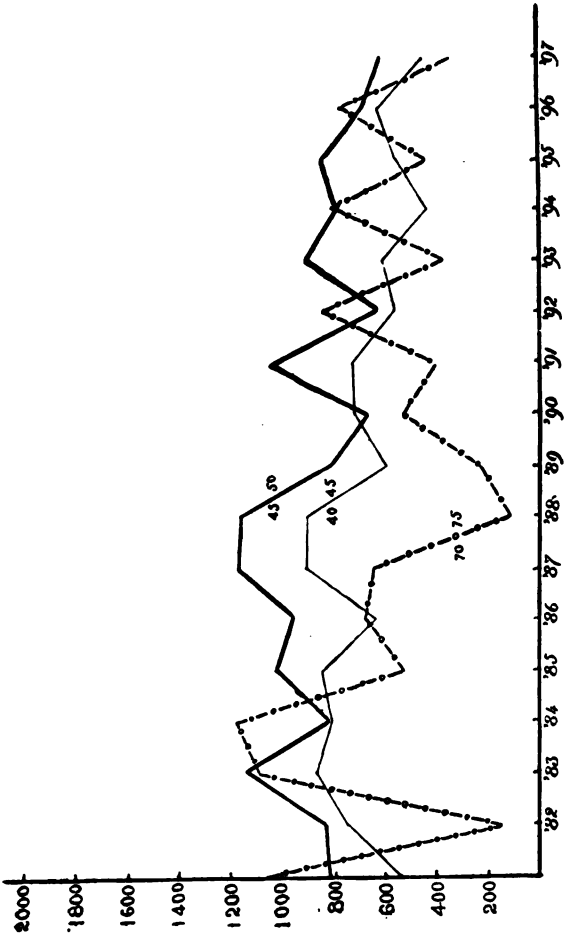
Males.

—	Under 5.	5 to 10.	10 to 15.	15 to 20.	20 to 25.	25 to 35.	35 to 45.	45 to 55.	55 to 65.	65 to 75.	75 to 85.	85 and upwards.
Skin	0.79	0.28	0.46	0.61	1.00	2.37	10.53	36.34	103.39	278.49	734.23	1650.20
Stomach	...	...	...	0.15	2.33	15.08	89.69	325.62	875.64	1530.94	1490.71	736.45
Rectum	0·13	..	0.46	0.91	4.83	10.94	35.90	142.54	393.57	718.54	826.19	668.26
Tongue	...	...	...	0.15	...	1.58	21.82	114.10	224.59	278.73	305.56	1772.94
Brain	3.30	3.38	2.49	2.90	3.33	6.31	10.66	16.50	20.25	13.34	2.97	—
Shoulder	0.26	0.14	0.29	0.61	0.83	0.89	1.01	2.11	4.05	8.72	14.83	13.64
Kidney and Adrenal	7.93	1.69	0.73	0.46	1.17	1.77	5.71	16.68	33.47	45.65	54.88	13.64

Females.

Skin	0.53	0.14	0.15	0.15	0.30	1.06	4.39	15.29	32.65	97.87	267.48	553.62
Stomach	0.13	...	0.15	0.15	1.04	12.38	79.27	278.78	678.29	1195.33	1255.77	834.48
Rectum	...	...	...	1.49	2.23	11.05	36.31	122.80	271.13	441.44	552.15	312.91
Uterus	0.26	...	...	0.45	3.30	61.99	337.25	746.34	967.16	1012.29	910.94	730.13
Breast	..	...	0.15	0.15	0.74	20.16	168.86	460.28	699.11	966.42	1407.23	3013.88
Tongue	0.13	...	...	...	0.15	2.21	3.68	7.64	17.98	42.18	49.41	24.07
Brain	1.32	2.10	1.76	1.64	2.97	4.33	9.85	11.55	13.49	10.65	6.45	—
Shoulder	...	0.28	0.29	0.45	0.30	0.71	0.95	1.30	4.02	4.91	7.52	8.02
Kidney and Adrenal	8.16	1.54	0.59	0.60	0.59	1.33	5.70	16.92	28.39	43.41	54.79	24.07

incidence of cancer. The suggestion is made that the senescence of individual tissues plays an important *rôle* in determining the initiation of cancerous proliferation in those tissues, and indicates a line of inquiry, at once biological and statistical, which promises the most valuable results.



Cancer of Uterus: Berlin, Deaths per 1,000,000 at Three Quinquennial Age-Periods, from 1881 to 1897. (Extracted from data supplied by the late Professor Hirschberg, Director of the Statistical Bureau, Berlin.)

We may attempt to elucidate cancer on the basis that the disease arises *de novo* in each sporadic case, in conformity with a law according to which cancer is a "function of senescence" dependent on circumstances innate in each species of animal, and on the laws peculiar

to and controlling their growth and length of life, and those of their individual organs. We may attempt to establish the existence of a common causal infective agent which is peculiarly subject to the same law. Statistical and experimental study has thus far only yielded evidence in favour of purely biological, as opposed to bacteriological, conceptions of the nature of cancer.

I hope the general statements I have made will be accepted as evidence that the investigation of the circumstances associated with the sporadic appearance of cancer, and the manner of the appearance of the disease in individuals, are together still capable of maintaining alive interest in statistics of cancer, and even of directing them into new channels. The value of statistical inquiries rests on the control they afford of the conclusions derived from experimental investigations, and on the indications they give of the most favourable points of attack, they are indispensable to the correct formulation of the problems requiring experimental solution. I cannot do better than conclude by expressing thanks to Dr. Tatham for the willingness with which he has placed the resources of the General Register Office at the service of the Imperial Cancer Research Fund, with a view to promoting this end. The collaboration of a national statistical office has not been vouchsafed to the same extent to similar inquiries out of England, and I trust that this collaboration may materially contribute to extracting the essential problem from the surrounding obscurity.

Discussion on Dr. Bashford's Paper.

The President: I should like to say that since the establishment of the Imperial Cancer Research Fund I have been connected with the Committee of that Fund, and in that capacity I have been brought (very fortunately for me) into very frequent relation with my friend Dr. Bashford.

I think that I shall be expressing the sentiments of the majority of my colleagues in this Society if I say that we are impatient (perhaps too much so) to learn, on the one hand, what new light Dr. Bashford's painstaking researches can throw on the nature and cause of cancer; and, on the other hand, whether to-day we are any nearer than formerly to the discovery of a cure for cancer.

To take the last point first, Dr. Bashford tells us that, as

regards cure, the consequences he has described of inoculating a mouse with a mite of tissue no larger than a pin's point show how rational is the modern surgical treatment of the disease. He points to the fact that the early surgical removal of the small piece of tissue at the site of inoculation prevents the diffusion of the disease, and the formation of secondary deposits in remote parts of the body. This evidence, in his opinion, demonstrates the necessity for prompt removal of the smallest growths, as is now constantly advocated by surgeons, and too often as constantly neglected by patients.

In consequence of the difficulty of recognising cancer in its earliest stages, Dr. Bashford sees little hope that within a reasonable time primary growths will be amenable to anything short of absolute removal. On the other hand, however, he says that from the fact that animals can be rendered unsuitable for the growth in their bodies of malignant processes, we are entitled to hope that eventually we may be able to so far enhance the power of resistance of the organism that the cells disseminated from the site of inoculation shall be unable to grow.

As regards the nature of cancer, Dr. Bashford assures us with confidence that much more is now known than was the case a few years ago. At all events, the way has been cleared by the demolition of theories of causation, which were rife only very recently. The manner in which carcinoma can be transmitted from individual to individual has now been so fully established experimentally as to be no longer in doubt. The experimental transfer of the disease presents a striking contrast in this respect—that transference can be effected very much more readily to young than to old animals. This is in absolute contradiction to what might have been—and, as a matter of fact, was—expected. This difference between young and old animals is, in Dr. Bashford's judgment, especially important in determining our conception of the etiology of cancer.

Dr. Bashford draws the conclusion that the greater frequency of cancer in later life is not due to increasing suitability for the growth of cancer; on the contrary, animals become less suitable for this growth the older they are. He tells us that, practically, every mouse can be successfully inoculated if the experimental conditions are favourable.

Finally, Dr. Bashford tells us that mice can be protected against successful inoculation by preceding inoculation of cancerous tissue from another mouse, but not from an

animal of another species. But the fact to which Dr. Bashford attaches supreme importance, and which I confess surprised me greatly, was this: that an equally high degree of protection can be conferred by the inoculation, not of cancerous, but of perfectly normal, tissue—healthy blood, in fact—from one healthy animal into the body of another of the same species. I am sure that we shall agree with Dr. Bashford that this one fact, which seems to me of startling importance, is, as he describes it, "pregnant with future possibilities."

I am sure we shall all agree as to the great importance of Dr. Bashford's paper.

DR. PAYNE: First of all, Mr. President, I must say how very much I am interested in Dr. Bashford's paper, and how greatly we are indebted to him for it.

I should like, if I may, to take up one or two points which seem to me of some importance.

The first point is the connection Dr. Bashford has established between cancerous growth and senescence, not only in man—of course it has been empirically known for a long time in man—but also in the lower animals . . . I agree, Sir, with the remark you made, that it is startling to find that young animals are as susceptible to receiving these noxious growths as older animals. This is not what one would expect. I suppose it will be explained in some way eventually, but at present it is somewhat difficult to reconcile it with other facts.

Dr. Bashford has this evening dwelt more upon points which have not been touched upon when this matter has been dealt with elsewhere; and, therefore, while we should be extremely glad to hear more about his personal contributions to the subject, we are glad to find that these other points are noticed.

He has made some interesting remarks as to the geographical distribution of cancer. Of course, it is very likely indeed that exaggerated views have been held upon that point; and it is also very likely that the enormous differences which at first sight appear are not found upon closer examination of all the factors. Again, as regards cancer among civilised nations, in an enormous country like India, where only a fraction of disease ever comes within medical purview at all, it is impossible to rely upon any figures which can be compiled.

Dr. Bashford has claimed for our own Registrar-General's department the first place for accuracy and precision, and

an intelligent consideration of all the factors bearing on the subject of registration of death and birth. He has also spoken in a not very complimentary manner as regards the statistics of Ireland. I wish it had been possible for him to say something about the statistics of Scotland; because, if I may say so, the Scottish returns are not nearly so good as those of England and Wales. I am always wondering how it is that such a great centre of intelligence as the Scottish capital has gone on for so many years with such very imperfect Registrar-General's returns: for such they are when compared with those of the English Office, which are founded upon the method established by Dr. Farr. The Scottish returns give us very little information on many points. With regard to the accuracy of diagnosis, I feel bound to make one statement in favour of Ireland. Dr. Grimshaw, who was Registrar-General for Ireland for a very long time, used to boast that his results were much more accurate than those of the English Office, and for this reason: that the Registrars in Ireland were all medical men, who took care, by questioning and so on, to get accurate returns of death. That was Dr. Grimshaw's position, and I am not able to criticise it. However that may be, it is very likely that the general level of medical practice in Ireland, not being so well paid, is not so high as in England; but I do not see that the statistics are capable of such very great errors as are attributed to them by Dr. Bashford.

As regards other European countries, their returns are certainly not as good as those of England. One cannot help thinking, however, that in a country like Germany, if they once recognise the great importance of proper registration, they will be able to carry it out in a very thorough fashion, because in Germany every person is known to the authorities. They know his age, where he lives, and all about him. I am convinced that if they once realised the value and importance of these returns, they could carry them out much more thoroughly than we can. And the same observation might be made with regard to Japan.

I do not know exactly why Dr. Bashford has entirely excluded the returns of Australia and New Zealand. I have not been in those countries, but I know many doctors there very well, and I believe their level of general medical practice is not at all low. There are good medical men there, most of them educated in London, although a fair proportion of them are now educated in their own country. I cannot see why their returns should not be accurate. And

if you read the reports, *e.g.*, of Victoria, New South Wales, and New Zealand, you will find that they are compiled with very great care, and that all such factors as age distribution (the distribution of age and population is not the same there as here) and sex distribution have been taken into account. The current return shows that in Victoria the mortality from cancer at certain ages was higher in the male than in the female sex, a state of things which is quite unknown in any European country, and which is explained by the fact that at these higher ages there are more men living than women in these places. The great care with which these exceptions have been stated is an indication of the care with which the returns have been prepared, and I cannot understand why Dr. Bashford has excluded them as untrustworthy.

With regard to another point, we know that in England and Wales, and also in Scotland (in Scotland the topographical reports are exceedingly minute), there are great differences in the registered mortality from cancer in different parts of the country. It was seen some time ago that these figures were not altogether satisfactory, because they did not take into account the age distribution in the several counties, but that point has been most carefully corrected by Dr. Tatham in all the recent reports. And what is the result? The result has been that the distribution of mortality from cancer has been changed. The same counties which formerly showed a high mortality from cancer in proportion to the death-rate now show a low mortality from cancer in proportion to the death-rate. . . . But remarkable inequalities still occur in different parts of the country, and I do not see that we can carry that any further. We must recognise that there are, in different parts of the country, many variations in the death-rate from cancer. And if so, why should not that be the case all over Europe? Why should we assume that, if we only carried out our registration returns with sufficient accuracy and investigated them closely enough, all differences would disappear and equality would result? If that were the case, cancer would be quite unlike any other disease; indeed, such a disease, unaffected by changes of time and space, is without a parallel. Therefore it does not seem probable (unless it should turn out that cancer is not in a certain sense a disease at all, but something in an entirely different category) that any such equality would be discovered.

I am exceedingly interested in cancer in early life. It

has been observed for a long time that the first few years of life give a much higher rate of mortality from cancer than the next five-yearly period. That appeared in statistics of England and Wales as long ago as 1851. In the statistics of age distribution of cancer for the period 1851-1860 it was found that the first year of life gave a higher rate of mortality than the next two five-yearly periods. I always thought that carcinoma was comparatively common in infants. I believe that if the figures for the first five years were further analysed, you would find that the great mass of cases come in the first two years, because that is the age when we find infantile sarcoma. From the Table on page 62, it appears that the difference between the distribution of cancer in the first two five-yearly periods of life is more than 8 per cent. in males and more than 6 per cent. in females. Now, if the kidney cases are taken away, the difference between the first five years and the second five years disappears. Now, malignant tumour of the kidney, although frequent in infants, is not frequent in later life, indeed it is very rare; it is a peculiar form of infantile growth. I must confess that the probable inference seems to me to be that these growths, which swell the figures for the period of infancy, are really congenital, or as good as congenital. It may easily happen that a tumour in the kidney in an infant will not be perceived until it is very large. I should think it probable that these tumours are, if not congenital, at least very nearly so, and therefore it seems doubtful whether they have any precise bearing on the question of cancer in general. The explanation of these kidney tumours has never appeared, I think.

Then there is the question whether sarcoma is to be regarded as cancer. It is true that sarcoma and cancer are always mixed up, and that some tumours of that kind appear to be related to the dissolution of certain portions of tissue in embryonic life. They are a very peculiar class of tumours altogether.

Well, now, with regard to the general results of Dr. Bashford's investigations in the London Hospital, they are most important and valuable, and I wish we had them rather more in detail. But I think it is clear that these figures cannot be compared with the statistics of death from cancer, as published. It must be remembered that these hospital figures represent cases of cancer, not necessarily deaths, and that the Registrar-General's statistics are compiled for entirely different purposes, and

include only those cases in which cancer is the cause of death. We do not know the number of cases which occur in the general population. Then, again, I think Dr. Bashford does not recognise sufficiently that the Registrar-General's certificates with regard to parts of the body do not state the primary seat of the disease; they do not profess to do so. The fact is that the death certificate is given to show what the patient died of. One example which will show the enormous difference is this: If you take the hospital statistics you find that cancer of the liver is hardly known. On the other hand, if you take the statistics of death-rate from cancer, you will find (I am taking the latest figures available) that in the last three years there were recorded 4190 deaths in males and 6935 deaths in females from cancer of the liver. In most of these cases the practitioner is probably perfectly right in saying that the patient died of secondary cancer. Another point connected with these two sets of figures is the distinction between accessible and inaccessible cancer. Accessible cancers are accessible to operations; and we know that owing to the enormous growth of surgery there are about ten times as many operations now as there were formerly, and that no cancer which is visible to the naked eye has much chance of escaping operation. As to cancer of the skin, I think we may hope that before long it will be a great rarity Personally, I should think myself very much to blame if I allowed a patient to die of cancer of the skin. Then, again, cancer of the breast leads to the breast being so completely exterminated that the one disease of which that patient is perfectly certain not to die is cancer of that breast, because there is no breast left there. Every organ that can be removed by operation is removed, and cancer in that organ is removed from the category of "primary" cancer. The number of operations that can be performed is increasing every year. Every year surgery is mowing down primary accessible cancers and preventing them from being regarded as causes of death.

There is one other point, and that is, I am sorry to find that the name of Dr. William Ogle has not been included amongst those who have been distinguished in this work. In 1884 Dr. William Ogle remarked on the supposed increase of cancer. He himself did not believe that there was really an increase, but that the apparent increase was entirely due to improved diagnosis. He made the remark also that the increase of cancer was more marked in the male than in the female, because cancer in the female was

accessible, whereas the greater portion of cancer in males occurs in inaccessible parts of the body, *e.g.*, the abdominal organs; this, therefore, was the reason, he said, for the apparent increase being chiefly in the males. He took up the subject again in 1890, and he then made the first attempt to give a full account of cancer as affecting different parts of the body. He initiated a method, but he feared to give the full results. Afterwards, Dr. Tatham undertook the enormous task of publishing the statistics for cancer in all parts of the body. Dr. Ogle thought that this was perhaps too large a job, but he took what he called a sample of cases, and made what would be called in mathematics "first approximations." Nevertheless, the result is well worthy of attention, because you will find that these first approximations sketched out the final result; indeed, they anticipated the result which has been worked out in later reports, that is to say, the comparatively rapid increase of cancer in internal organs and its comparatively slow increase in those that are accessible to operation. Dr. William Ogle's results were recognised and stated by my friend Dr. Newsholme, but since that time they seem to have dropped out; I think, therefore, it is fair to say that, however well these things have been carried out by others, the origination of this idea, *i.e.*, the importance of observing whether cancer was accessible or inaccessible, and the bearing of that fact upon diagnosis as well as upon statistical results, was entirely due to Dr. Ogle.

Personally, I am very much indebted to Dr. Bashford for his most interesting paper.

SIR SHIRLEY MURPHY: I should like to join in the expressions of thanks which have been conveyed to Dr. Bashford for his able and interesting paper.

One point that interested me was whether Dr. Bashford's investigations were throwing any light upon the question whether improved medical knowledge would tend to increase the record of deaths from cancer or reduce them. One knows that error can creep in in two ways; but there will be, as it were, a fictitious loss in regard to the cases not diagnosed and which were really cancer, and a fictitious gain as to those wrongly diagnosed as cancer. I think Dr. Bashford's paper, and especially the Table relating to the London hospitals, shows that with improved knowledge there will be a great tendency for the figures to increase; that is to say, that looking at the accessible and inaccessible and intermediate cases of cancer in these

Tables, one sees that the proportion of total accessible cases is as 100 to 67, whilst the proportion of total inacessible to wrongly diagnosed is as 100 to 6. Inasmuch as improved medical knowledge would tend to put the inaccessible on a level with the accessible, it would tend to increase the amount of cancer and would tend to increase the number of deaths from cancer.

Dr. Bashford has insisted very much on the need of investigating the amount of cancer in specified areas. I may point out that in considering the amount of cancer in well-to-do London districts and poor London districts, when correction is made for sex and age, one finds that the incidence of cancer for rich and poor is very much the same.

There is only one other small point. Dr. Bashford spoke about the comparison between a series of figures for the West and a series of figures for the East; but he has not mentioned one series which to my mind is the most interesting laboratory of statistics on the subject of the pathology of deaths in the East. It is very likely that he has taken account of it, but on the chance that perhaps he has not done so, I would like to draw attention to the very excellent statistics that are constantly being produced in the laboratory at Hong Kong. If Dr. Bashford has already come into touch with them, perhaps he would say whether anything definite has been brought out on that subject. You have there the peculiar fact of a limited population living under a law by which every death not certified by a European has to be examined in the laboratory, and there are in that way two thousand bacteriological and pathological examinations in the course of a year. This state of things is, I believe, unique, and it would be interesting to know what is the death-rate in that very typical Oriental population from this particular cause as compared with a European population. The statistics are admirably condensed by Dr. Horne, who was one of Dr. Bullock's students at the London Hospital.

Dr. Newsholme: I am sure we are all greatly indebted to Dr. Bashford for his very important paper. We all knew that Dr. Bashford was an extremely competent pathologist, but we did not know that he was equally competent in another capacity, namely, in that of a statistician.

One is bound to agree with the limitations that he has made so far as the application of statistical methods to the

discovery of the cause of cancer is concerned, though possibly he may have a little overstated those limitations. But I think we should remember the fact that by means of the statistics which he and his colleagues have initiated, we are able to say now, in the first place, that civilisation is not an essential factor in the causation of cancer. We are able to say again that we get cancer in fish and in the lower animals, and that the incidence of the disease in cattle and mice, for example, is practically in the same proportion as in man. Those are extremely valuable results to have been obtained from statistics, because they indicate that civilisation is not a main factor, and also that a meat diet is not necessarily an essential factor, since you get cancer occurring amongst animals like cattle, which eat no flesh, and also amongst races like Hindoos, who live chiefly upon rice, As a matter of fact, therefore, statistics have borne a rather important part in the results that, up to the present time, have been achieved; and though perhaps pathology will bear a still more important part, we must not allow statistics to be entirely set aside. Then, again, the fact that statistics have shown that cancer appears to be a disease of senescence is a very important result; and one of the most interesting results of the Cancer Research Fund so far has been the extension of the idea of senescence, not only to the whole being, but also to the particular tissues and organs of the body. The extreme instance given by Dr. Bashford of chorion epithelioma is a very striking instance indeed. I think, therefore, it may be said that if statistics have so far borne the greater part in that investigation of cancer, it is because of the failures of pathology.

With regard to the question of cancer houses, though undoubtedly the results do appear sporadic in the accounts given in medical journals with regard to cancer houses, the accounts given also indicate a presupposition as to the pathology of the disease, viz., that it is infectious. The writers of these accounts undoubtedly forget that they are dealing with very small figures, and that there may be a run of coincidences. They forget how long the arm of coincidences may be—how, for instance, if you set a sufficient number of persons tossing halfpence you will eventually get a man who will toss 1000 heads without a break. When one remembers coincidences like that, one is able to attach very little importance to numbers of cases in particular houses. . . . If those cases occurred alongside of our pathological knowledge that cancer was an

infectious disease, they would have much more importance.

As to the amount of cancer and the question of the increase of cancer, this is, I believe, a question of how the doctors enter the certificates. They may enter the certificate properly, and they may not. A doctor will enter a death, say, as due to abdominal tumour, and the certificate is sent to the Registrar-General. The President then writes to him and asks what was the nature of the tumour. The doctor then comes to the conclusion that it may have been a cancer, and he sends a letter to say that it was a cancer, and that death gets entered as cancer. But, after all, this is only a guess on the part of the doctor, and the positive guess may be as wrong in its definiteness as the original indefinite certificate was. Indeed, the original indefinite certificate may have been more trustworthy than the ultimate more definite statement. I am not saying that in any spirit of obstruction to the system of letter writing from the Registrar-General's office. I think it is a good system, and I am sure we all appreciate it; but in the process of education of the medical profession which is going on, the comparability of medical certificates is being destroyed, so far as these certificates are concerned, and we have to do with certification on different lines to what it was before.

I venture to differ from Dr. Bashford on one point, which I do not think he can really have considered fully. Cancer is not a rare disaase ; it is a very common disease indeed. It is much more common than typhoid fever, and nearly as common as pulmonary tuberculosis.

With regard to the Irish figures, I agree with Dr. Bashford's failure to believe in their trustworthiness. This fact was brought out some years ago with some clearness by a paper written by Mr. King and myself. One factor which was brought out in that paper was that the population of Ireland was an older population than that of England, although the percentage of average age had become lower in the last two consecutive decades. Another reason is, that owing to the smaller number of deaths in hospitals, there are fewer investigations of the cause of death. On the whole, then, I think one must reject the Irish figures as comparatively untrustworthy.

I should like to express my gratitude to Dr. Bashford for his admirable paper, and for the very suggestive lines of work which he has undertaken.

DR. F. W. ANDREWES: I am afraid I have nothing to add to the discussion as regards statistics of cancer, but I should like to coincide fully with what Dr. Payne has said as to the incidence of cancer during the first quinquennial period of life. Probably a large number of these cases are sarcarmatous.

DR. DAWSON WILLIAMS: I did not intend to speak; but as you are kind enough to ask me, I would like to make one point, and that is, to take this opportunity of emphasising what Dr. Payne has said. I believe that unless a sharp distinction is made between these things that we call sarcoma that occur in infancy and the remainder, a considerable mistake will be made; and it occurs to one that by comparing the character of these sarcomas, their pathological characters generally, with those of cancer in later life, something might be learned. The question which arises with regard to this is, whether obsolescence and senescence are exactly the same things, and whether obsolescence is not a period of growth: all through fœtal development there is this process of obsolescence constantly going on. Therefore, if we confuse obsolescence with senescence, we may be going wrong in that.

There is one obsolescent organ which has a chance of proceeding to senescence, and that is, the vermiform appendix, but I do not think it is the primary seat of cancer.

I should like to ask, if senescence is very important, why is it that cancer of the stomach and intestines is not very uncommon in middle life and in advanced life, because it is a common observation that when a man loses every other passion, he retains the desire to eat and the power of digesting his food.

DR. BASHFORD: Mr. President and Gentlemen: In the first place I should like to thank you very much for the sympathetic manner in which you have listened to my somewhat scattered remarks.

It was, I think, quite impossible for me to refer to the statistics of Australia, of Hong Kong, and of other places. I am very familiar with Mr. Cook's valuable statistics for Victoria; but, as they did not seem to me to bring out any point which the statistics of Europe did not bring out equally well, I left them alone.

I have listened to Dr. Payne's remarks with great pleasure, more particularly because he was somewhat critical. I do not think it would be wise for me to reply to

him in detail, because whatever material I have excluded has been excluded because I did not think it was of sufficient importance.

There is one point to which I should like to refer. I do not wish to imply that I have been deliberately depreciating the quality of the statistics compiled in Prussia as compared with those in England. But when comparing different decennia the development and increased accuracy of Prussian statistics in recent years must be remembered. The fact that the number of cases of cancer recorded has absolutely increased, is a matter of great importance; but it is not very long ago that many Prussian towns introduced certification of the cause of death by medical men. I was only instancing Prussia as conveniently comparable, by reason of the state of things there, with a country like Ireland.

I think it is very probable that Dr. Payne, Dr. Andrewes, and myself are all in entire agreement as to cancer in children, viz., that these tumours are of a complicated structure, and that the growths on the kidney, etc., already referred to, are probably sarcarmatous.

With regard to the question of separation of sarcoma and carcinoma, to which several speakers have referred, it is a very difficult matter to separate them. Clinically, they are one and the same thing. The medical man guesses at sarcoma just as he guesses at carcinoma. . . . For registration purposes they are the same thing. In hospital, at any rate, sarcoma, although relatively more frequent at birth and in early years than carcinoma, presents exactly the same phenomena as cancer. Dr. Murray and myself attempted to find out whether the same thing applied to the general population. We took selected areas and worked out the death-rate, and we found that for the general population the sarcoma increases with increasing years in exactly the same proportion as carcinoma.

I am very much indebted to Dr. Payne for drawing my attention to Dr. Ogle's work on the relation between accessible and inaccessible cancer, of which work I had a vague knowledge.

Then, in regard to Hong Kong, I am aware of the figures which are supplied there; I have been able to obtain them through the Colonial Office. But, unfortunately, cancer figures only to a very small extent in these returns, so far as they have come to my hands. The patients appear to be to a large extent young people, and the cases seem to be investigated more from a bacteriological point of view

(with special reference to plague, and so on) than with reference to the occurrence of the particular conditions. So far as the returns go which I have received from Hong Kong (I have not received the figures for this year), there was nothing very striking in their figures. The mere fact that there was nothing anomalous was probably the reason why they did not make any more impression upon my mind.

I should like to thank you for the attention which you have given to my paper, and the interest you have shown in this work. I should like also to remind you of the fact that this work can hardly be regarded as my personal work. I have had associated with me not only Dr. Murray, but also Dr. Cramer and Mr. Bowen. We are all associated with the Imperial Cancer Research; we are the servants of a corporation which enjoys opportunities such as has never yet been enjoyed by any group of persons engaged in the investigation of cancer; and if we have been able to advance the knowledge of cancer in any way, it is because it has been found possible to organise the inquiry upon a scale not hitherto attempted.

I think the profession as a whole should give due credit to the Royal Colleges of Physicians and Surgeons for the laborious method in which they have set about instituting this inquiry.

RECENT RESEARCHES INTO THE EPIDEMIOLOGY OF MALTA FEVER.

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(*Read: Friday, February 15th*, 1907.)

THE subject of this evening's Paper is "Recent Researches into the Epidemiology of Malta Fever." In this place it is not necessary to go into any detail in regard to the history or symptoms of this fever, but a few introductory words will not be amiss.

Malta fever, as you are all aware, is a disease of long duration, averaging four months, but in some cases dragging out its weary length for one, two, or even three years. The temperature-curve is characterised by extreme irregularity, fresh exacerbations of fever being frequent. Another prominent feature of this fever is the presence of symptoms of a rheumatic or neuralgic character. Few marked cases pass through their course without the occurrence of painful and swollen joints, or neuritis in various nerves, which combine with the prolonged temperature to bring the patient to a condition of extreme anæmia and debility, from which recovery to health is slow.

I think I have said enough of the nature of this fever to impress upon those of you who are not familiar with it the importance and severe nature of the disease under discussion.

HISTORICAL.

Let me say a word in regard to the history of Malta fever. This fever has naturally been chiefly worked at by Army medical officers, who have come in contact with it among the garrisons in Malta, Gibraltar, Cyprus, or at Netley Hospital. Those interested in its history should read the old accounts of it by Marston, in 1863, and Veale, in 1881. At that time it was generally considered to be malarious in origin, and was usually returned as remittent fever; but the most severe cases were often returned as enteric, and the very mild as febricula or simple continued

fever. In 1887, the specific micro-organism, the *Micrococcus melitensis*, was discovered, which effectually separated it from other continued fevers, and it found a place in the third edition of the *Nomenclature of Diseases*, published in 1896. In 1904, as the incidence of this fever among the garrison of Malta had increased to a marked extent, the Royal Society, at the request of the Admiralty, War Office, and Colonial Office, undertook its further investigation, and sent out a small commission to Malta for that purpose. This commission has been at work during the summers of 1904, 1905, and 1906, and the Royal Society has already published seven volumes of reports. It is a summary of the work done by this commission which forms the subject of this Paper.

Geographical Distribution.

In regard to the geographical distribution of this fever, a few words will suffice. One curious thing is, that it has almost or quite disappeared of late years from Gibraltar, where some years ago it was very prevalent. In the Mediterranean it undoubtedly occurs in such places as Tunis, Algiers, and Alexandria, as well as in Malta. It also occurs in such widely-separated places as South Africa, India, China, the Philippine Islands and America. It has, therefore, a world-wide distribution, although nowhere does it seem to occur in such numbers as in Malta.

In regard to other etiological factors, such as the influence of age and sex, of occupation, length of residence, climatic conditions, etc., I must refer you to the Reports, where these matters are entered into very fully. Permit me, however, to glance briefly at one or two points which I consider of interest.

Social Position.

Here we come against a curious fact, and one which it was impossible to explain until lately. It may be stated, broadly, that the better the social position the more the liability to this disease. Officers and their wives and families, living in large, airy, and clean houses, suffer more frequently than the men in their more crowded barrack-rooms. In fact, the risk of the military and naval officers to take this fever is more than three times as great as in the case of the men.

This higher incidence among the officers cannot be explained by sanitary conditions, by convection of the

disease by mosquitoes, or by inhalation of infected dust, or any of the theories usually held; as the officer is, if anything, less exposed to these influences than the men.

Climatic Conditions.

The climate of Malta, as you are aware, is extremely hot and dusty from about the middle of June to the middle of October, while the winter months are correspondingly bleak and wet. Now, although the number of cases of Malta fever do show a marked increase in summer, yet it is a disease which is prevalent all the year round: one-third as many cases occurring in the coldest and rainiest months as in the hottest and dustiest. Another fact of interest is, that if we study the incidence of Malta fever in individual years, we are struck by its irregularity: a large number of cases suddenly appearing in February or December, or other of the cold and rainy months. It was found difficult to reconcile these facts with mosquito or dust theories of propagation.

Distribution of Malta Fever among the Civil Population.

Until recently it was supposed by many of us that this fever was restricted to the inhabitants of the cities surrounding the Grand Harbour. This was in the days when the theory was held that the virus was carried in sewer air or other foul gases. As the Grand Harbour in those days was a huge cesspool—the drainage of the cities falling into it—there was some excuse for a belief in the theory. Malta fever is now known to occur in every part of Malta, and, in fact, the very general distribution of the fever is very striking. It is not the cities round the harbours which are struck most heavily, some of the inland towns and villages showing a much greater incidence.

It is evident, then, that the incidence of Malta fever cannot depend upon sanitary conditions, since the greatest variety exists, from the paved, drained, swept Valletta, to the inland towns and villages where the most insanitary conditions prevail. It cannot depend on the water supply, since there is often a larger number of cases in towns with an excellent supply of pure water than in towns which depend for their supply on shallow wells. The cause must be sought in something which affects all classes and all conditions of life.

Distribution among the Garrison.

Next I would draw your attention to the prevalence of this disease among our soldiers and sailors in Malta, in order to impress upon you the importance of this disease to the State. Among the soldiers—who average, as a rule, about 8,000—there is an average yearly incidence of 37.6 per 1,000, or 312 admissions to hospital every year for Malta fever.

Among the sailors there in an incidence of 28.55 per 1,000, or about the same number of admissions to hospital as among the soldiers.

Now, as the average duration of this disease may be put down at four months, it means that some 624 soldiers and sailors are in hospital 120 days, which makes 74,880 days of illness. What an amount of personal suffering and loss to the State this sickness and the subsequent invaliding entail it is impossible to estimate, but the mere pecuniary loss must be very considerable.

Micrococcus melitensis.

It is evident from the foregoing account that little light has been thrown on the etiology of this disease by a study of sanitary conditions, effect of climate, age and sex, length of residence, occupation, food or water-supply, etc. It is therefore necessary to turn to the laboratory to see if anything can be discovered from a study of the micro-organism which causes the disease. The *Micrococcus melitensis* has been described so often that it is not necessary for me to describe it minutely. Suffice it to say that it is very minute, that it grows outside the body on artificial media, and that it can be distinguished from other micro-organisms by suitable tests.

The members of the commission entrusted with the laboratory work set themselves to study how this micro-organism leaves the body, how it behaves outside the body, and how it is able to again gain entrance to the body.

How does the Micrococcus melitensis *leave the Body?*—It is important, of course, to find out how a parasite leaves the body, as this may throw light on the mode of infection. Many experiments were made to try to discover it in the expired air, in the saliva, expectoration, sweat and scrapings of skin of patients; and finally it was decided that the principal path by which this micro-organism leaves the body is by way of the urine. It is true it also leaves the

body by way of the blood, by the agency of mosquitoes and other biting insects, but this only rarely and in extremely small numbers. The urine, on the other hand, sometimes contains the Micrococci in enormous numbers, though as a rule they are scarce, ranging from three or four to as many hundreds per cubic centimetre. The commission examined several thousand samples and found the Micrococcus in 10 per cent. This excretion of the parasite in the urine, taken in conjunction with its resistance to drying, was looked upon by the commission as a very probable factor in the spread of the disease, and many experiments were made on this hypothesis.

Life of the Micrococcus melitensis *Outside the Body. Vitality of the Micrococcus.*—Many experiments were made by the commission, the results of which went to show that this micro-organism is fairly resistant to external influences. It can exist in a dry condition, in dust or clothing, for two to three months. It lives in tap-water or sea-water for about one month. Even in urine which has decomposed and become markedly alkaline, it can live for a week. Exposure to direct sunlight kills it in a few hours.

Habitat of the Micrococcus Outside the Human Body.—Many attempts were made to discover this parasite outside the body. As the theories in vogue named insanitary conditions, sewer air, dust from infected places, the water of the harbour, etc., as causing this fever, diligent search was made in every likely place to discover this microbe, but up to the present with no success.

How does the Micrococcus gain Entrance to the Body?—It is on finding the correct answer to this question that the success of an investigation such as this probably hangs. Does the parasite gain entrance by way of the alimentary canal, by the lungs, through mucous membranes, or through the skin? In other words, is it conveyed from the sick to the healthy by means of food or drink, by contaminated dust, or by blood-sucking insects?

In trying to find out a means of stamping out a disease, it is important to try to narrow down the paths of infection. As long as yellow fever was thought to be spread by contact—infected clothes, food, water, etc.—nothing could be done. As soon as it was discovered that it was spread by a particular species of mosquito, the problem of prevention was simple. In the same way in Malta fever: if it can be spread by contact, contamination of food or water, by the inhalation of dust, sewer air, etc., it will be impos-

sible to do more than recommend the ordinary established rules of hygiene. But, on the other hand, if the mode of spread can be narrowed down to some one path, then stamping out the disease becomes possible. Let me, then, shortly discuss the experiments made by the commission to solve this question.

By Contact.—This is important, as questions of segregation, evacuation, and disinfection of barracks depend on this mode of infection. Experiments were made by placing monkeys in more or less intimate contact, and it was found that if the contact was quite intimate, infection does take place. If, on the other hand, the contact is less intimate, so that contamination of the food by infected urine was prevented, infection did not take place. It was concluded that the monkeys probably took the disease by having their food contaminated by the urine of their sick neighbours, and that therefore contact resolved itself into a feeding experiment.

As it is very unlikely that man has his food so grossly contaminated as in the case of the monkey, it is improbable that infection takes place, except very rarely, in this way.

In regard to this question of conveyance by contact, there is one argument against it which seems to me unanswerable, and that is, that thousands of cases of Malta fever have been invalided home to England and treated in our naval and military hospitals without, as far as I am aware, a single case of the fever arising among the patients, orderlies, or nursing sisters. We may therefore conclude that contact with Malta-fever patients, or the handling of infective clothing or discharges, is not the path by which the Micrococcus gains entrance to the body.

By Dust contaminated by the Micrococcus melitensis.—For some time it was considered probable that this would prove to be the common method of infection. The fact that the Micrococcus withstands drying for a long time, the dusty nature of Malta, and the probability that gross contamination of the surface of the soil takes place by infective discharge rendered this view likely.

Experiments were made to put the theory to the test. Dust was artificially contaminated with Micrococci, and blown about a room in which monkeys were confined, or blown into their nostrils or throat. Several of these experiments were successful. It was therefore proved that dust artificially contaminated with *Micrococcus melitensis* could give rise to the disease. This, however, was no proof

that this mode of infection occurs in Nature. The artificially-contaminated dust contained myriads of Micrococci. Under natural conditions they could seldom be numerous, and the powerful Maltese sunlight would tend to kill them off rapidly. The dust blown about by the wind must also dilute the Micrococci to an enormous extent; so that it is only possible to conceive of a Micrococcus here and there in a vast quantity of dust. Experiments were therefore made with dust contaminated with urine, in order more closely to resemble natural conditions. The commission made many experiments on these lines, but in no case with a successful result. Dust collected from suspicious places and blown about the cages, sprinkled on food or injected under the skin, also gave negative results.

The conclusion was therefore come to that conveyance of the infective germ by means of contaminated dust could only rarely, if ever, give rise to the disease.

By Way of the Alimentary Canal.—As it is most important to ascertain without a shadow of a doubt whether an infective micro-organism can enter by way of the alimentary canal, many feeding experiments were made. It had long been known that the smallest quantity of the Micrococci introduced under the skin, or applied to a scratch, would give rise to the disease in man and monkeys, but some previous work had cast doubts on infection by the mouth.

I need not bring the details of these experiments before you, but need only state that it has been abundantly proved that Malta fever can be conveyed to healthy animals by way of the alimentary canal. Even a single drink of fluid containing few Micrococci almost certainly gives rise to the disease.

By Mosquitoes or other Biting Flies.—As already mentioned, the theory had been advanced that Malta fever, like yellow fever and plague, might be conveyed by blood-sucking insects. The fact that the Micrococci are frequently found in the peripheral blood, although it must be confessed in very small numbers, gave some colour to the belief. The commission, therefore, fully investigated this question, and made numerous experiments with the different species of mosquitoes found in Malta, and also with other blood-sucking insects.

The results went to show that this mode of conveyance of the Micrococci from sick to healthy animals, if not absolutely negatived, can only be of the rarest occurrence.

Up to this point, then, the commission had shown by

experiment that the most probable way the Micrococcus gained entrance to the body was by the alimentary canal, and therefore by some infected food or drink. There was no evidence that contact, inhalation of infective dust, or mosquitoes, play any prominent *rôle*. But, on the other hand, the epidemiologists could see no reason for suspecting the water-supply or any particular food-stuff.

Infection by means of Goats' Milk.

At last a discovery was made which threw a flood of light on the obscurities, and seemed to explain the epidemiological features of the disease. This was the remarkable discovery that the goats in Malta act as the reservoir of the virus of this fever. The discovery came about in this way. In an investigation of this sort, it is part of the work to examine the various surrounding animals, to find out if any of them are susceptible to the disease. The monkey was the only animal which was known to take the disease naturally, although some of the laboratory animals, such as the rabbit and guinea-pig, could be made to take the infection by various expedients, such as, for example, intracerebral inoculation. In this way the goat came under observation. The goat is very much in evidence in Malta, and supplies practically all the milk used. Flocks of them wander about the streets from morning till night, and are milked as required at the customers' doors. It must be confessed the commission had little hope that an examination of these animals would yield anything. As a matter of routine, however, several goats were inoculated with the Micrococcus, and the result watched. There was no rise of temperature, no sign of ill-health in any way; but in a week or two the blood was found to be capable of agglutinating the specific micro-organism. Even then, the goat seemed such an unlikely subject for Malta fever, the observation was in danger of lapsing. Nothing more was done for several months, when, by accident, the matter came up again, and it was decided to repeat the inoculation experiments. A small herd was procured for the purpose, and, as an ordinary precautionary measure, their blood was examined before inoculation. Much to the surprise of the commission, several of them were found to react naturally to the agglutination test, and this led to the examination, and the discovery of the *Micrococcus melitensis* in the blood, urine, and milk. Some thousands of goats in Malta were then examined, and the epoch-making discovery was made that 50 per cent. of

the goats in Malta responded to the agglutination test, and that actually 10 per cent. of them were secreting the Micrococci in their milk. Thus the long and tedious investigation of this fever was beginning to bear fruit. Monkeys fed on milk from an affected goat, even for one day, almost invariably took the disease. At this time, curiously enough, an important experiment on the drinking of goats' milk by man took place accidentally. This is the case of the s.s. *Joshua Nicholson*, which has been fully described by Staff-Surgeon Clayton, in Vol. VII of the *Reports of the Commission*. Shortly, the story is as follows:—In 1905 the s.s. *Joshua Nicholson* shipped sixty-five goats at Malta for export to America. The milk was drunk in large quantities by the captain and the crew, with the result that practically everyone who drank the milk was struck down by Malta fever. There is no need for me to go into the details, as these can be read in the *Report*. I may add, however, that sixty of the goats (five having died) on arrival in America, were examined, and thirty-two found to give the agglutination reaction, while the *Micrococcus melitensis* itself was isolated from the milk of several of them.

This epidemic of Malta fever on board the *Joshua Nicholson* furnishes, in my opinion, the clearest proof possible of the connection of Malta fever in man with the Maltese goat.

Another proof of this connection is given by Major Horrocks, the Sanitary Officer at Gibraltar, and published in Vol. V of the *Reports*. Twenty years ago, Malta fever was very common in Gibraltar, but since that time the incidence has gradually lessened, until it finally disappeared completely in 1904. Horrocks has made the curious and important observation that this disappearance of Malta fever from Gibraltar is associated with the disappearance of the Maltese goat. He says that, in 1883, practically all the goats on the Rock were Maltese, and at that time regular shipments of goats from Malta to Gibraltar took place. *Pari passu* with the withdrawal of grazing passes and the increase in the cost of shipment, the importation of goats from Malta ceased, and goat-keepers replaced their stock, partly by importation of Spanish goats and partly by breeding.

Here, then, at last, has been discovered a mode of infection which explains many of the curious features in the epidemiology of Malta fever; the irregular seasonal prevalence, the number of cases which occur during the winter

months, when there are no mosquitoes and little dust. It is true there are more cases in summer, but this may be explained by the temperature being more favourable for the multiplication of the Micrococcus in milk that has been set aside, and to the fact that more milk and cream is used for fruit, in ice-creams, etc. It explains the liability of the officer to attack being three times as great as in the case of the private soldier, since the former consumes much more milk in various ways than the latter. It also explains the isolated epidemics which sometimes occur at any season of the year in institutions or in messes, such as that published by Johnstone in Vol. II of the *Reports of the Commission*, where a sergeants' mess was severely struck while the men living in the vicinity escaped.

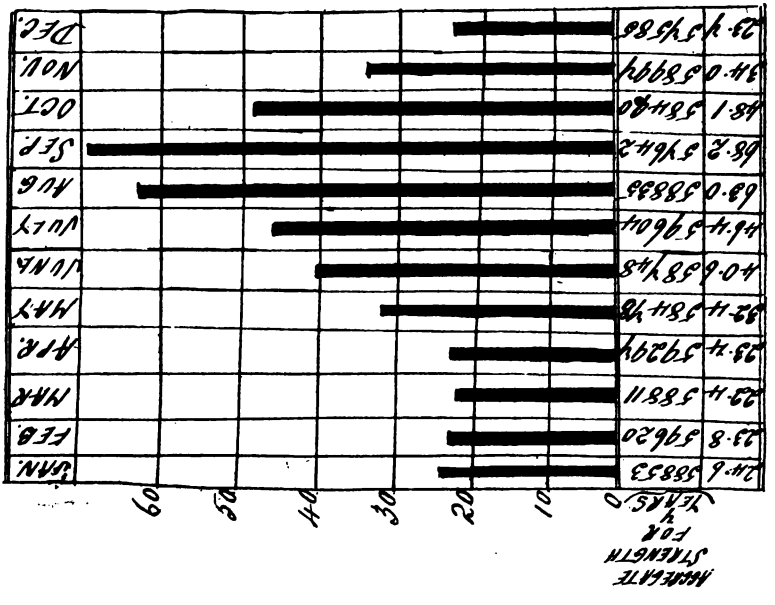
Results of Measures directed against the use of Goats' Milk.—Preventive measures, as a result of this inquiry, were first begun in Malta in June, 1906. Of course, much opposition and prejudice were met with at first; but, by dint of argument and explanation, most of the regiments and military and naval hospitals agreed to banish goats' milk from their dietary. The result is very striking, as is shown in the following charts, which give the number of cases of Malta fever among the soldiers in the garrison, before and after the preventive measures came into action.

The preventive measures, it must be repeated, only came into practical use about the beginning of July, 1906, and a remarkable diminution in the incidence is at once seen. Broadly speaking, the cases dropped to one-tenth of what would have been their normal number. It will also be noted that 1906 began badly, there being an average incidence of 31.0 per 1000 for the first six months, against 27.6 per 1000 for the years 1899 to 1905.

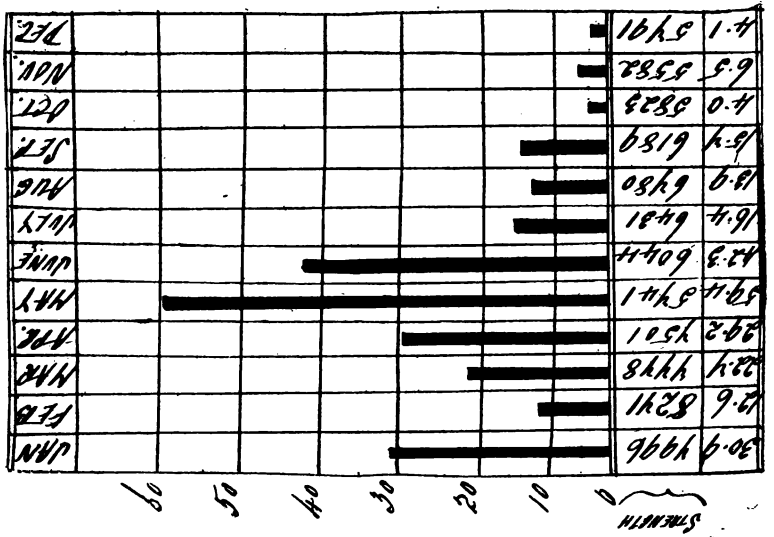
Another striking example of the benefit of this simple preventive measure is given in the case of the Royal Naval Hospital, Malta. This hospital is a fine modern building, situated in extensive grounds, surrounded on three sides by the sea, with excellent drainage and water-supply, and beautifully kept. In spite of these advantages, this hospital has been in bad repute for years, on account of the number of cases of Malta fever which broke out among its inmates. According to Staff-Surgeon Clayton, who enters very fully into this question in his report, one-third of the cases of Malta fever which occur in the Navy can be traced to residence in this hospital. The goats supplying the hospital

Monthly Prevalence: Ratio per 1000 of Strength, expressed in terms of an Annual Ratio.

1899 to 1905.

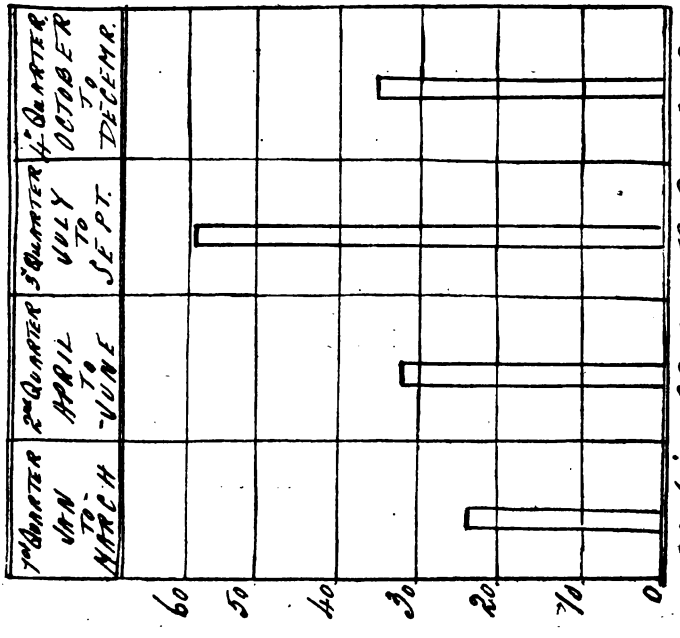


1906.

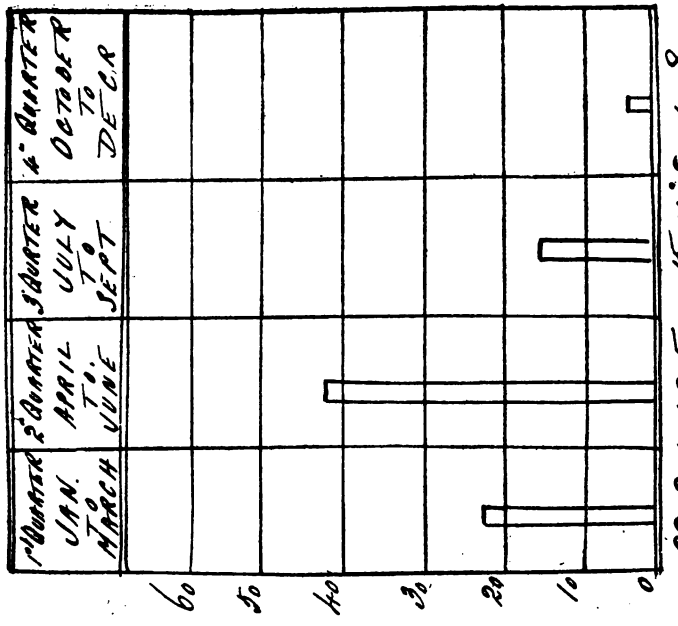


Quarterly Prevalence: Ratio per 1000 of Strength, expressed in terms of an Annual Ratio.

1899 to 1905.



1906.



Half-Yearly Prevalence.

1899 to 1905. 1906.

with milk were examined, and several of them found to be excreting the Micrococcus in their milk. Goats' milk was forbidden, and from that date not a single case has occurred or can be traced to residence in this hospital.

Conclusions.

Taking all these facts and arguments into consideration, there is, I think, reasonable ground for the hope that Malta fever will now disappear from the Army and Navy in Malta, and some 70,000 or 80,000 days of severe illness be blotted out from the yearly medical reports of the Army and Navy. This much-to-be-desired result, which, in my opinion, must come off if the Maltese Government only take the necessary measures, will change Malta from one of the unhealthiest and most dangerous stations in the British Army to one of the most salubrious; and you will agree with me that the Royal Society and the members of the commission are to be congratulated on the successful issue of the investigation.

Discussion on Colonel Bruce's Paper.

The President: Gentlemen,—You will all agree, I am sure, as to the interesting and important character of the paper we have just heard. I think that to those of us who live most of our time in England, and do not see much Malta fever, the most important and the most hopeful portion of the paper is its conclusion, where Colonel Bruce tells us of the measures which, if carried out (and they are certainly practicable), will render our great military and naval station at Malta one of the healthiest in the world. Eighty thousand days of sickness per year is a very large proportion, and if a great deal of this can be saved, one cannot help thinking that it is the duty of those in authority to incur the necessary expense, even though it may be heavy.

There is no question in my mind that the thanks of all medical men and epidemiologists are due to the Royal Society, and to the gentlemen who composed the Commission, for their action in this matter.

Colonel Macpherson: I did not come here with the intention of entering into the discussion on this subject, because I am sure we all acknowledge that Colonel Bruce is practically our sole authority on the subject of Malta fever, and I was not aware of the arguments he was going to bring forward, except the one which we now recognise is the most important of all, namely, the question of goats' milk. I should only like to ask him whether he is perfectly satisfied, and whether the Commission of the Royal Society have satisfied themselves that it is only the Maltese goat that is the agent for the propagation of Malta fever. We know the disease is prevalent all along the Mediterranean coast, in Spain, in Italy, in Greece, and in Syria. I believe it has recently got the name of Mediterranean fever, because it is distinctly associated with the Mediterranean littoral. We know that that littoral is associated with the goat, which is the principal, indeed, almost the only, milk-giving animal. Colonel Bruce brings forward Major Horrocks's statistics for Gibraltar, and says that when goats ceased to be imported from Malta to Gibraltar the fever disappeared from Gibraltar; one is thereby led to believe that it is only the Maltese goat that can propagate the disease.

I do not think the facts that Colonel Bruce has brought forward with regard to Gibraltar are sufficiently conclusive.

I was in Gibraltar in the same capacity as Major Horrocks —as Health Officer—from 1890 to 1897, and I noticed at that time the sudden disappearance of both Malta fever and continued fever. Now Colonel Bruce says that Malta fever was very prominent twenty years ago; but Malta fever did not appear in any of the records twenty years ago. We only had records of simple continued fever. We called everything continued fever that was not of short duration. I do not think it is right to say that because that simple continued fever suddenly dropped in Gibraltar at a certain time, that therefore it was Mediterranean fever that disappeared. That sudden drop in simple continued fever occurred in the year 1886, and it was extremely sudden. (I am talking only of the statistics of the military population, of course we had no statistics of the civil population to help us in any way.) With regard to the military population, the admission rate of continued fever up to 1886 was almost continually something like 700 per thousand per annum; it was a constant ratio, and did not fluctuate much. Then suddenly it dropped, and in 1887 (I am open to correction as regards the actual year) it dropped down to about 100 per thousand and remained at that rate for a long time afterwards. During the time I was Health Officer it kept on getting lower. Goats existed and were very numerous; they were, in fact, the sole source of milk supply, except a few cows which were kept for special cases and families. Goats' milk is brought to the houses in the same way as in Malta, as Colonel Bruce has just graphically described to us. Now these goats were all kept by Maltese; they were not kept by Spaniards. I never knew myself the difference between Maltese and Spanish goats. What I should like to ask Colonel Bruce is: how far are we to accept the Maltese goat as alone the cause of Maltese fever, or how far must we allow the Spanish goat and other goats to cause it? If the Spanish goat or the mongrel goat on the Rock at Gibraltar do not cause the disease, and if Malta fever has disappeared from Gibraltar on account of the Maltese goat having disappeared, then I think that there is room for further investigation as to whether it is only the goat that exists in Malta that is able to propagate the fever.

COLONEL MELVILLE: There is only one point upon which I should like to make a remark, that is, as to the prevalence of Malta fever in India. Malta fever has been reported

from the Punjaub several times, and especially from some stations in the Punjaub. Now the goat exists there, but goats' milk is not drunk as goats' milk, and certainly the greater part of the milk we have there is cows' milk. If Colonel Bruce has any information as to Malta fever in India and its connection with the goat there, I should be glad to know what it is.

CAPTAIN KENNEDY: There are two things that especially interest me in these reports. (I take it for granted that these reports are published since the Colonel has read this paper.) I should like to refer to one thing which is not reported here. With reference to the cases of Malta fever occurring in hospitals, a great many seemed to occur among cases of venereal disease, and that struck me as being a very important point of investigation. I therefore went into the subject of the prostitutes there, and at the same time Dr. Eyre came out and helped me in the investigation. We found that a great many of them were suffering from Malta fever, and we came to the conclusion that it was quite possible that the soldiers might contract the disease through this agency.

Then there is another point, with regard to the urine. The excretion of the *Micrococcus melitensis* in the urine is very peculiar. It occurs just when the temperature is coming down to normal, and it occurs in very great quantities. This excretion may go on for a very long period of time; it may last for a year or even eighteen months. This is a very important factor, I think, when we take into consideration the epidemiology of the disease. I do not think (as Colonel Bruce says) that it will be an easy matter to eradicate the disease from Malta when you take into consideration such a fact as that.

DR. FRANKLIN PARSONS: I should like to ask whether the micrococcus in milk could not be destroyed by boiling, and if so, whether boiling the goats' milk might not be a simple and easy precaution?

I should also like to know how long the goat continues to yield milk contaminated by the Micrococcus, and whether it can be told by the agglutination test when a goat has passed through this fever; if a goat that has once passed through the fever is protected against it, that goat's milk might apparently be used. Assuming the thesis that the disease is mainly spread by milk, these two expedients

might possibly help to check the disease in places where it is impossible to prohibit the use of milk altogether.

DR. MEREDITH RICHARDS: I should like to ask Colonel Bruce how he can explain the case of Malta fever that occurred in Croydon last summer. The patient was brought into Croydon Borough Hospital, and she was supposed to have enteric fever, but she was not suffering from enteric fever, as was clear from the reaction to the serum agglutination test. The history of the case was as follows: The patient was a domestic servant. She had left Malta on July 2nd with her mistress, who had suffered from Malta fever at Malta. On the 10th July her mistress had a relapse, and my patient attended this mistress on and off until August 1st. On August 1st she had symptoms which were supposed to be those of enteric fever, but which were undoubtedly those of Malta fever. She was in hospital for three or four months, and she had several typical relapses. The interesting point of the case is that either the incubation period was longer than that of Malta fever generally, or else it is sometimes possible (contrary to the statement in the paper) for the disease to be contracted from person to person in England.

DR. CARNEGIE BROWN: I think we must all admire the excellent way in which Colonel Bruce seizes the salient epidemiological points in connection with Malta fever.

I should like to say, in connection with the remarks of the last speaker and of Colonel Melville, that most men who have seen much of diseases in the East Indies are familiar with a type of fever that prevails there, which is extremely like Malta fever in its general clinical features. There is the same long-drawn course, the same ladder-like rises of temperature, the same graduated descent through similar periods of reaction, and the same exacerbation and repetition of all the phenomena. There are no parasites to be found in the blood, and the disease is not amenable to treatment by quinine or any other anti-periodic. Most of these cases drag on for many weary months. Treatment does not influence the disease in any way, and the fever gets well, as it is colloquially expressed, by wearing itself out. In my own experience of the disease I have not seen any cases exhibiting the particular inflammation, the large number of leucocytes, or any other of the symptoms which are described as accompanying Malta fever. But this fever affects all races, all ages, and both sexes, and it

is by no means uncommon in children. It was natural, I think, that when the nature and the character of Malta fever was first elucidated by Colonel Bruce, that this affection, which presented such remarkable clinical features, should be supposed to be Malta fever; that a considerable amount of attention should be attracted to it, and that attempts should be made by means of agglutination tests and by leucocyte counts to determine its actual relation. Speaking for myself, I came across two occurrences of *Micrococcus melitensis*, one of which came from Netley, and the other from Kasauli. I found that in 80 per cent. the Micrococcus was agglutinated by the blood serum with a dilution of 1 in 50. I think this was the general experience, and the belief then became general that not only was Malta fever extremely prevalent, but that this was an extremely good and decisive test and criterion for its existence. That belief, I think, was fairly generally accepted, but doubts very soon began to arise. It was soon declared that a fever which is known in the East Indies as Kala-azar was Malta fever—that Kala-azar was epidemic Malta fever. But most of us who were familiar with Kala-azar knew that this type of fever was not only different, but that there could be no possibility of confusing the two diseases. One is more severe, and is marked by enlargement of the spleen, whilst in the other the spleen is not enlarged. It was upon the evidence of leucocyte counts and upon agglutination that Kala-azar was declared to be Malta fever. But the demonstration of the actual nature of Kala-azar, viz., that it is a protozoal infection, has demolished that contention. At the same time it has given a severe blow to the reliability of agglutination tests in the case of the *Micrococcus melitensis*, and, consequently, to the belief that this prevalent fever of the East is Malta fever. The report of the Mediterranean Fever Commission of 1905 has further accentuated the points of difference, for it is certain that the disorder of which I speak frequently occurs in people who do not take goats' milk in any form.

I do not know if I have made myself clear, but the points I have ventured to emphasise are that there is at least one prevalent fever in the Eastern tropics which bears a strong clinical resemblance to Malta fever, that its agglutination reactions with *Micrococcus melitensis* may be identical, that differential leucocyte counts may also show an altogether remarkable similarity, but that it is not and cannot be true Malta fever. The pathogenic Micrococcus

has not being isolated, and it is certain that the fever is of frequent occurrence amongst people who do not take milk—goats' or cows'—in any form. The inference is that too much reliance should not be placed on the diagnostic value of agglutination and differential leucocyte tests. The belief that Malta fever is indigenous and prevalent in the East Indies must be abandoned for the present.

THE PRESIDENT: I am sure you will wish me to say to Colonel Bruce on your behalf that the Society is very much obliged to him for his interesting and instructive paper.

Before I call upon him to reply, I should like to ask him whether the disease is attended with very heavy fatality? Also, does the fatality vary with the season or locality?

COLONEL BRUCE: In answer to the President's question the mortality of Malta fever is comparatively slight, and may be put down at 2 per cent. It is a comparatively non-fatal disease, but it makes up for this by its long duration and painful character.

Colonel Macpherson asks if it is only the Maltese goat which propagates Malta fever. To this I would answer "No," as probably all goats are susceptible. It may, however, be the case that only in Malta is there such a widespread infection of the goats.

In regard to his statement that the disease is prevalent all along the Mediterranean coast, in Spain, Italy, Greece, etc., I am not sure that in this he is correct. Shaw travelled along the south coast of France and along Italy, and nowhere did he find any trace of the disease. We do know that it occurs in Tunis, Algiers, and Alexandria, but these places are much frequented by Maltese and Maltese goats.

I must refer Colonel Macpherson to Major Horrocks's paper on the disappearance of Malta fever from Gibraltar *pari passu* with the disappearance of the Maltese goat; but, in my opinion, a fairly good case has been made out. Probably other factors came into play, but I have no doubt the Maltese goat played a prominent part. Major Horrocks is still working in Gibraltar on this subject, and will probably give us many more interesting observations on this important question.

In regard to Colonel Melville's question as to the connection between Malta fever and goats' milk in the Punjaub,

in India, I am sorry we have very few new facts to go on at present. No doubt when Major Lamb has finished his present plague investigation he will find an opportunity of returning to the question of the causation of Malta fever in India. Of course the Maltese goat may travel far. When I was at the Victoria Falls, on the Zambesi, eighteen months ago, I met Sir Charles Metcalfe, the Consulting Engineer to the Cape to Cairo Railway. He told me they had introduced Maltese goats into Rhodesia and with them Malta fever. In the same way the disease may have been introduced into the Orange River Colony, where it doubtless exists, as Dr. Strachan has recently shown. Did any of the Rhodesian goats find their way into the Orange River Colony, or is the disease indigenous there? In my paper I have shown what a determined effort the Americans made to introduce the disease into the neighbourhood of Washington.

Captain Kennedy is evidently of opinion that there may be other important factors in the spread of this disease than goats' milk. He may, of course, be right in this; but as practical men, now that we have discovered an undoubted and most dangerous source of infection, it is our duty to concentrate our attention on it, and by making the Maltese goats healthy, to see what effect that has on the incidence of the disease. If after the disappearance of the infected goat many cases of Malta fever still occur, then we must take up again the investigation of its etiology.

In answer to Dr. Franklin Parsons, I beg to say that, of course, boiling the goats' milk will kill the *Micrococcus melitensis*. The difficulty is to get the natives to take this simple precaution. In the Naval Hospital it was supposed that the milk was boiled thoroughly, yet the man in charge of the laboratory took the milk one day and found the living Micrococcus in it. The boiling may be done as a rule, but the herd comes late one morning and there is a hurry for the milk, and the Maltese servant decides that he will take the milk as boiled already.

It is not exactly known how long the goat continues to excrete the Micrococci in the milk, but this certainly takes place for a long time—months, or even years.

Dr. Meredith Richards asks me to explain the case of Malta fever which occurred at Croydon last summer. There has been some evidence brought forward of late to show that the incubation period may be much longer than the fifteen or twenty days which is usually accepted. Major

McCulloch treats on this subject in his report, and I would refer Dr. Richards to it. In my opinion a long incubation period would best explain his case.

Dr. Carnegie Brown took up the question of the reliability of the agglutination test in Malta fever. I would refer him to a paper of Bassett-Smith's on this subject in the Reports. Shortly, I would state that in the hands of a careful, qualified observer, I consider the test practically reliable.

VARIATIONS IN THE AGE-INCIDENCE OF MORTALITY FROM CERTAIN DISEASES.

By Sir SHIRLEY MURPHY.

(*Read: Friday, March* 15*th*, 1907.)

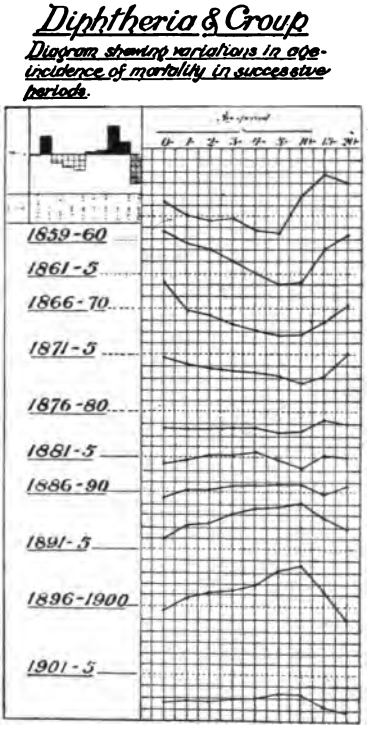
At the request of your Secretaries, I am proposing to submit for your consideration a series of diagrams showing change in the age-incidence of mortality from certain diseases. The subject has been from time to time discussed in reports I have presented to the London County Council; but although it is not entirely new, I hope the diagrams will be found to be of sufficient interest to the meeting to justify me in occupying a part of the evening in their exhibition.

I wish, in the first instance, to state how these diagrams have been constructed, in order that they may be perfectly intelligible. The method of construction is the same in each instance. The mean death-rate at each age in the whole period under consideration is taken as a standard, and the death-rate at each age of each quinquennial or decennial period is stated as a percentage above or below the mean of the whole period. Thus the death-rates at the several ages over the whole period are represented by a straight line, and the excess or defect of the death-rates at these ages in each quinquennial or decennial period forms a curved line above or below the mean. It is obvious that by this method any deviation from a straight line represents variation in the age-incidence of mortality.

The first diagram (Fig. 1) which I will ask you to look at is based upon the deaths in London from diphtheria and croup, from the period 1859 to 1905. The first period, represented by a curved line, relates to the years 1859 and 1860, while all other lines relate to quinquennial periods. The curves of 1859-1860 and 1861-1865 closely resemble each other. The line is bent with the convexity downwards, the ages 4, 5 to 10, and 10 to 15 being in the second period, the three lowest points in the curve.

The period 1859-1865 was one of epidemic prevalence. The next three quinquennial periods are periods of decline of prevalence; but it will be seen that this decline has been obtained not so much by decline at the ages I have mentioned as by decline at ages below and above those ages, so that the line representing the period 1876-80 is almost a straight line. The periods 1881-85 and 1886-

Fig. 1.



90 are periods of increase of prevalence, and the increase has been much the same at each age, although it will be noted that in 1881-85 the ages 2, 3, and 4 are a trifle above the mean, and in 1886-90 the ages 1, 2, 3, 4, 5 to 10, and 10 to 15 are also above the mean. There is, indeed, a slight tendency in both these periods for the line to become curved with the convexity upwards. In 1891-95 the recent epidemic in London was at its height; there was increase at each age, but this increase was most

marked at ages 4, 5 to 10, and 10 to 15. In 1896-1900 there was some decline, but the mortality from this disease was still much above the average, especially at the ages 5 to 10 and 10 to 15. In 1901-5 the death-rate at all ages was lower than it has been since the deaths from diphtheria have been separately stated by the Registrar-General, and the line has now become almost straight, with a slight tendency

Fig. 2.

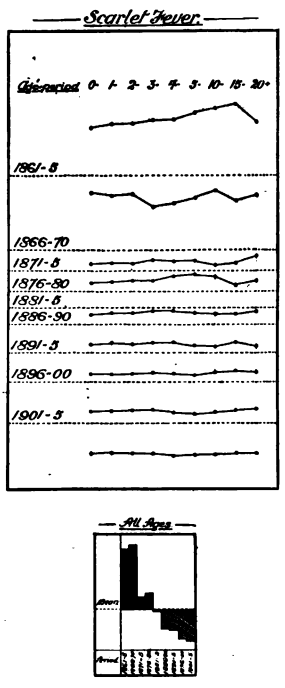
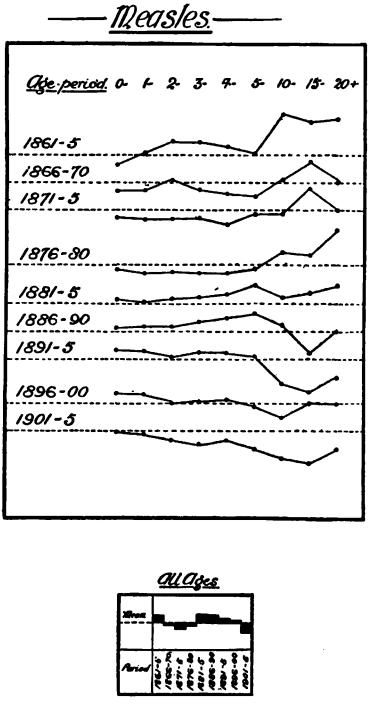


Fig. 3.



for the decrease to be less manifested at ages 5 to 10 and 10 to 15 than at the other ages.

There has, therefore, been a change in age-incidence, which there is reason for thinking is rhythmical; but the whole story is not yet complete, for we need the periods 1906-10 and 1911-15, or indeed still later periods, to enable us to see whether the lines which they will provide will resemble those of 1866-70 and 1871-75. Possibly, however, there will be less conspicuous curves than in these years, owing to the greater aggregation of children in

school leading to increased incidence of mortality at the school age. It is noteworthy that the increased incidence on ages 4, 5 to 10 and 10 to 15 began when there was decline in the all-ages death-rate. I think this may probably be a natural increase, although it may have been accentuated by increase in aggregation of children at school. However this may be, I should expect to find the first evidence of recurrence of epidemic prevalence of diphtheria in increase of relative incidence upon the ages 4, 5 to 10, and 10 to 15.

The scarlet fever diagram (Fig. 2) is only able to show a story of decline during practically the whole period for which the figures are available. There is, however, a greater tendency for the lines to become straight in the later periods than in the earlier. The line for the period 1861-65 shows greater relative incidence on the ages 4, 5 to 10, 10 to 15, and 15 to 20 than that of any others; and again in 1876-80, when there was some increase in mortality at all ages, this was especially manifest at ages 4, 5 to 10, and 10 to 15. Of course, it needs to be remembered that the periods between epidemic prevalences of scarlet fever may be much longer than in the case of diphtheria, and that the time for the minimum incidence on the ages mentioned has not yet come: otherwise a depression of the curve in the last period or two might have been expected; unless, of course, as the result of greater aggregation of children, at ages 4, 5 to 10, and 10 to 15, the depression in the curve at those ages, which might otherwise have occurred, has been obscured. All that can be said is, that there is some suggestion in the last two curves of depression at these ages.

The measles diagram (Fig. 3) tells much the same story. In 1861-65, a period of high mortality, this was exceptionally manifest at ages 2, 3, and 4. (The figures for ages over 10 are comparatively small, and no great importance can attach to them.) With decline of mortality the line becomes more nearly straight. With increased mortality in 1881-85,and 1886-90, the increase is manifested especially at ages 3, 4, and 5 to 10; and then with decreasing mortality at all ages this special incidence becomes less evident.

The whooping-cough diagram (Fig. 4) closely resembles that of measles. Here, again, the figures for the higher ages are small, and apt to yield exceptional results. With slight exceptions, there has been decline in the period represented. The curve which is seen in the line 1861-65

becomes flattened out in subsequent periods. The small increase in mortality at all ages in the period 1876-80 does not appear to have materially affected the curve of those years.

The diagram of enteric fever (Fig. 5) is interesting, because, while there has been decline in the death-rate at all ages during the whole period represented, with very slight exception in 1896-1900, there has been increasingly greater

Fig. 4.

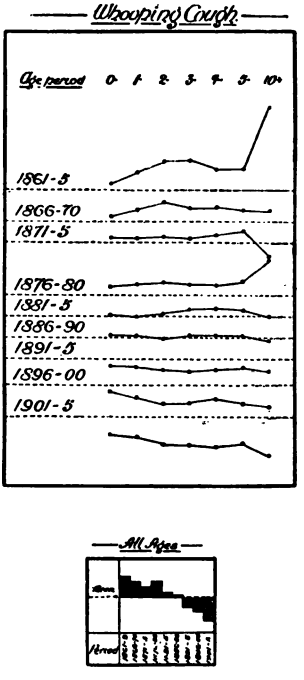
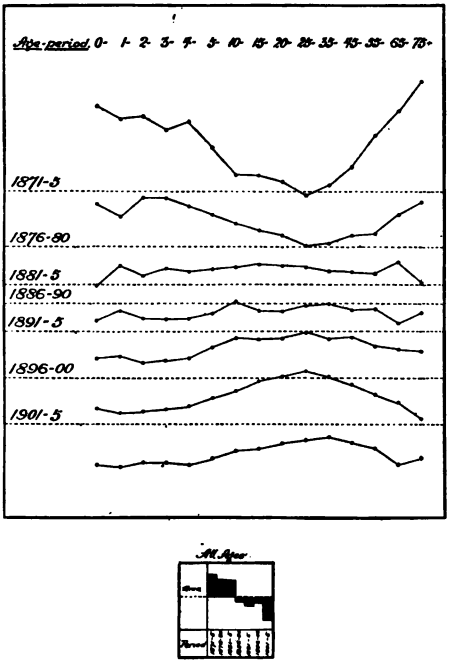


Fig. 5.

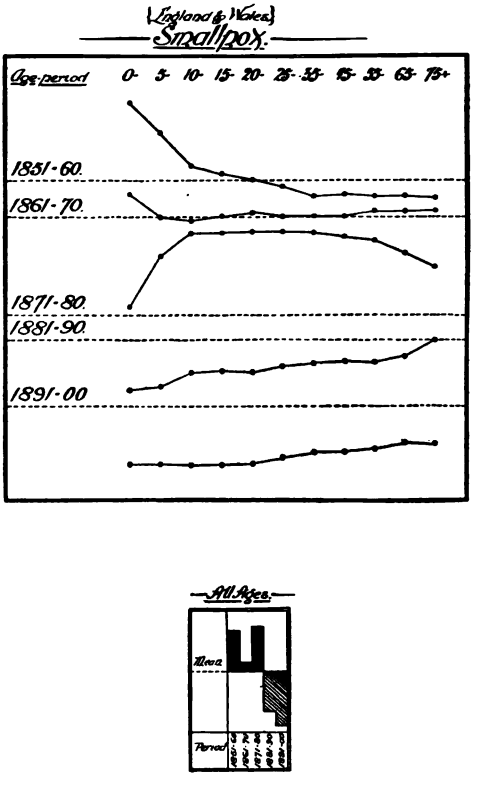


relative incidence on the age-period 25 to 35, and on the ages which immediately precede and follow that age-period. The diagram shows that these ages have not participated in the general decline anything like so much as the others. In the period 1901-05, however, the line is straighter than it was in 1896-1900. Although it is quite conceivable that the age-incidence of mortality from this disease would be affected by alteration in the opportunity for infection to reach man by particular channels, in view of what is seen in

the diagrams relating to the other diseases, I cannot deny the possibility that this change is a natural variation. It will be recollected that the diphtheria diagram manifested increase of incidence on age-periods 4, 5 to 10, and 10 to 15, with decline of mortality at all ages.

For the purposes of a diagram representing small-pox mortality, I have been obliged to abandon London, and use

Fig. 6.

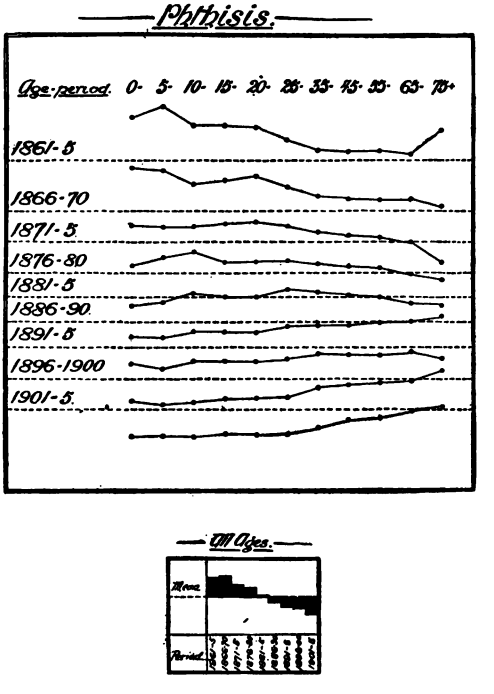


figures relating to England and Wales, so as to avoid the error which would result from the removal of cases of small-pox from London to districts outside where the deaths were registered. It is, of course, impossible from this diagram (Fig. 6) to learn what is the natural behaviour of small-pox in respect of age-incidence, on account of the disturbing effect of vaccination. It is, however, interesting to compare the incidence on the age-periods 0 to 5 and

5 to 10 in the two epidemic periods 1851-60, and 1871-80, and to observe that in the two later decennia, in the absence of epidemic prevalence, the lines lose their curvature and become more nearly straight.

The diagram for phthisis (Fig. 7) shows, of course, general decline of mortality from this disease, and shows also how much more marked this decline is at the younger ages

Fig. 7.

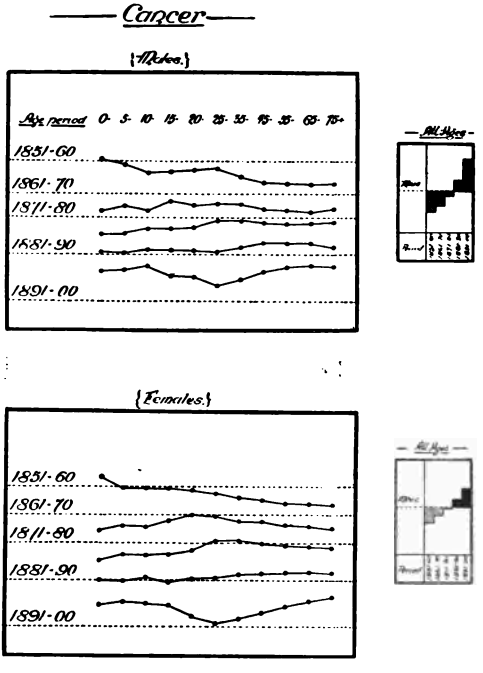


than at the older ages. It gives no indication of that behaviour of the curves which is noticeable especially in the case of diphtheria, but is suggestive of decline of mortality owing to successive additions by birth of a more resistant race.

The cancer diagram (Fig. 8), based on the figures for England and Wales, is in the main interesting, as showing behaviour which, I think, can only be explicable on the hypothesis of change in nomenclature. It will be seen that the incidence on ages below 25 years was in the second

and third decennia relatively less than in the first, while on ages above 25 the incidence is increasing. Further, the incidence on age 25 to 35 is in the second and third periods relatively increasing. In the fourth period the line becomes practically straight, but in the fifth period the incidence on ages 25 to 35 becomes relatively less than on other ages. The actual incidence on age 25 to 35 has, however, remained practically constant throughout the whole 50 years.

Fig. 8.



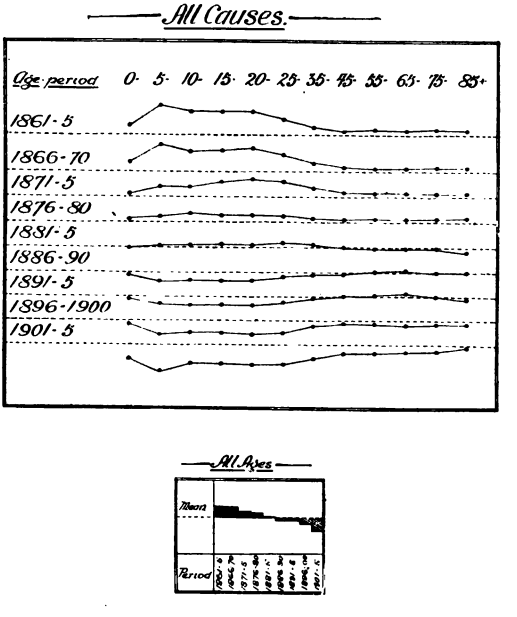
The last of this series is the diagram relating to "all causes" (Fig. 9.) It closely resembles the diagram for phthisis, but differs from it in exhibiting a tendency for the mortality of the first year of life to be maintained in greater degree than that of subsequent ages. This is no doubt in some degree due to the mortality from measles and whooping-cough being especially maintained in the first year of life, but is probably largely due to the more complete registration during later periods of deaths of infants who survive their birth but a short time. There is here,

also, suggestion of the birth in successive periods of a more resistant race.

I have said little concerning the effect which change of nomenclature, better diagnosis, etc., must have had on the diagrams; and indeed only mention it now to protect myself from the suggestion that I have not had it in my mind. I have preferred to present the diagrams based as they are on the actual records of the Registrar-General.

I think, however, in the case of the infectious maladies,

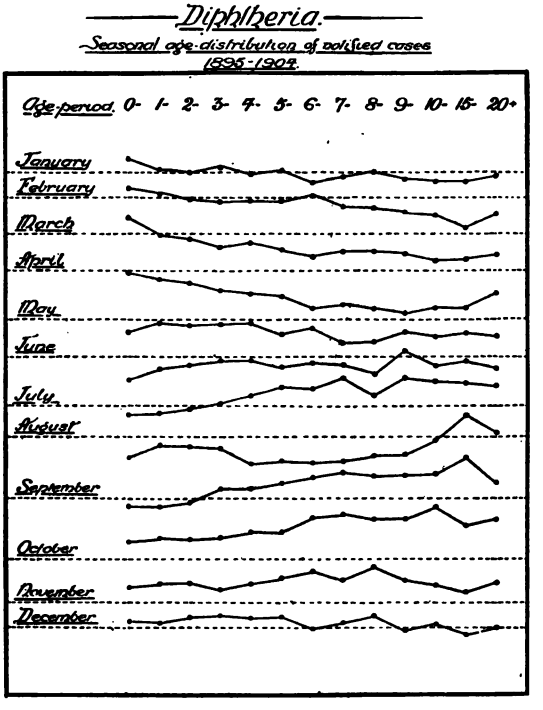
Fig. 9.



scarlet fever, diphtheria, measles, and whooping-cough, that variations in the age-incidence of mortality occur as a natural phenomenon, not improbably as the result of variation in virulence, and affected also no doubt by such influences as difference in opportunity of acquiring infection, and perhaps in small degree by differences in the proportion of persons at the several ages rendered immune by attack in antecedent periods. That these variations are not the same as those seen in the other diagrams tends to confirm this view.

Apart from the variations which occur over long periods, variations can also be shown to occur as the result of season. The last two diagrams I have to exhibit show this in respect of diphtheria and scarlet fever. It will be seen that in the case of diphtheria (Fig. 10), the incidence of attack on the ages 5, 6, 7, and 8 increasingly declines until

Fig. 10.

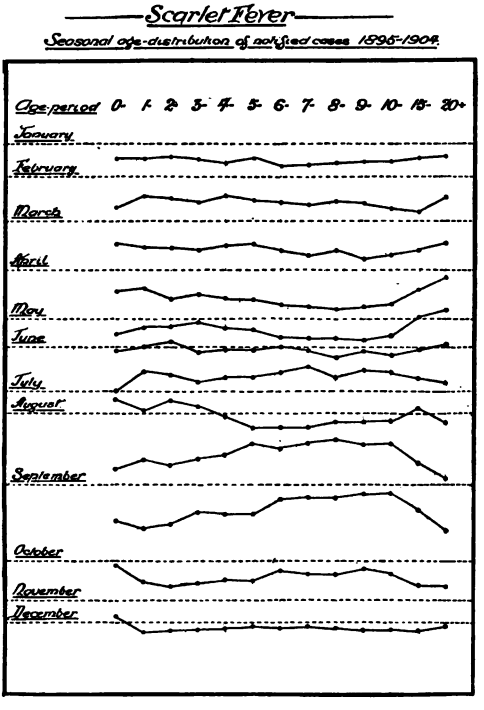


April, after which it increases until August, when the increase is interrupted by the school holiday. It is again manifest in September and October, and then again declines.

The diagram relating to scarlet fever (Fig. 11) shows practically the same behaviour, except that the decline at the ages mentioned is continued to May.

In June the line becomes practically straight, and in July, with the seasonal increase which then becomes manifest, there is some tendency to convexity of the line at the school ages. In August the effect of the

Fig. 11.



summer holiday is conspicuous, the decline at the school ages being marked, while in September and October the increased incidence at these ages is especially pronounced. In November, with the decline of general prevalence, the line again becomes less curved, and it is practically straight in December.

AN OUTBREAK SIMULATING INFLUENZA IN AN INSTITUTION.

By W. A. BOND, M.A., M.D., Medical Officer of Health of the Borough of Holborn.

(*Read: Friday, March 15th*, 1907.)

I HAVE called this an outbreak simulating influenza on account of the similarity to an epidemic in the East Herts. District, which occurred in 1904-1905, and was reported upon by Dr. R. A. Dunn, Medical Officer of Health, East Herts. and Essex Combined Districts, and Dr. M. H. Gordon, and was called "An Epidemic Simulating Influenza."

These epidemics, simulating influenza, are very interesting from the epidemiological standpoint, and I hope this Paper will lead to an interesting discussion as to whether this outbreak and similar outbreaks were really influenza or not. They are also of much interest to doctors generally, and to medical officers of health in particular, on account of the varied rashes that occur, some simulating the scarlatinal rash, others the rash of measles. Moreover, some cases simulate enteric fever, and have been so notified.

At the beginning of the outbreak, on the 21st October, 1906, at the institution (St. Giles in the Fields and St. George, Bloomsbury, Receiving Home for Children), there were thirty-six children and a staff of five, consisting of a matron, nurse, assistant-nurse, and two housemaids.

Of the thirty-six children, nineteen had well-marked symptoms, and the majority of the remaining seventeen were not really well, although they had no treatment for any particular symptoms. Of the staff, the matron was the only one that had well-marked symptoms.

On the 17th October eighteen children were admitted to the home from the Holborn Workhouse, Shepherdess

Walk. Prior to this no children had been admitted for a month, viz., three on the 18th September. From inquiries I have made at this workhouse, I find that amongst the children sent out on the 17th October there had been cases of doubtful illness during the month. One of them (E. H.. female, 11 years) had headache, fever, sore throat, scarlatinal rash on the chest and back, and was removed to another ward on the 29th September, and afterwards to an isolation ward, and did not return to the general ward until the 11th October.

The following are the details respecting the twenty well-marked cases, for which I am much indebted to the matron and nurse of the institution:—

1st. R. M., male, 8 years. Admitted to the Home on the 10th August, 1906. Illness began on the 21st October (*i.e.*, four days after the admission of the eighteen children from the Holborn Workhouse). This patient had high temperature, running from eyes and nose, and was covered with a measly rash. The patient was isolated the same day, and sent away on the following day to the Holborn Infirmary as suffering from measles. Dr. McLearn, the medical officer of this infirmary, kindly showed me the patient's card, and from it I found that the patient had a temperature of 98 deg. on the evening of the 22nd, and the temperature was sub-normal, viz., 97 deg., on the following morning. The patient also suffered from bronchitis. The rash was not medicinal. (Chart shown.)

2nd and 3rd. K. B., female, 3 years, and C. P., male, 4 years. Admitted 16th July, 1906. Illness began 23rd October, 1906. Sickness, feverishness, running from the eyes; lasting about four days.

4th. L. S., female, 3 years. Admitted 23rd June, 1906. Illness began 24th October, 1906. Sore throat, sickness, fever and great weakness; lasting three or four days.

5th. W. M., male, 12 years, brother of No. 1. Admitted 10th August, 1906. Illness began 25th October, 1906. Headache, sickness, sore throat, temperature 103 deg. at 5 p.m., and rash. Patient was sent away the same day to the Holborn Workhouse, where he was thought to be suffering from measles, and was at once sent to the Holborn Infirmary. The following day, the 26th, the patient was

sent to the North-Eastern Fever Hospital, notified as scarlet fever. I afterwards received information from the Fever Hospital that the patient was not suffering from scarlet fever, but tonsilitis, and was discharged on the 26th November, 1906. The rash was *not* medicinal. (Chart shown.)

6th. J. R., male, 13 years. Admitted 17th October, 1906. Illness began 27th October, 1906. Headache, sore throat, and a slight rash on face and neck. The highest temperature (102.6 deg.) was reached on the evening of the second day of the illness, the 28th, and the patient was isolated for five days from the 27th. (Chart shown.)

7th. T. S., male, 9 years. Admitted 17th October, 1906. Illness also began 27th October, 1906. Headache, very bad throat, temperature, p.m., 103.6 ; slight rash on body and chest. Very restless and delirious nights, of 27th and 28th. Very thirsty, and watery stools for first two days Isolated for five days from the 27th. (Chart shown.)

8th. A. F., male, 7 years. Admitted 13th August, 1906. Illness began 27th October, 1906. Sore throat; temperature 102 and 103 on the first day; running from eyes. Patient was isolated for three days from the first day of illness. (Chart shown.)

9th. L. L, female, 11 years. Admitted 21st July, 1906. Illness began 1st November, 1906. Headache, swollen throat, feverishness, and bad eyes. Illness lasted about four days.

10th. M. S., female, 11 years. Sister of No 7; admitted 17th October, 1906. Illness began 1st November, 1906. Headache, sore throat, feverishness, and general weakness; lasting for four or five days.

11th. M. F., female, 4 years. Sister of No. 8; admitted 13th August 1906. Illness began 2nd November, 1906. Sickness and weakness for two or three days.

12th. M. K. E., matron. Illness began 5th November, 1906, with very bad throat and tongue, high temperature, running from eyes and nose, and excessive weakness. These symptoms lasted for eight days, the first few days being very acute.

13th. E. P., male, 3 years. Admitted 23rd June, 1906; isolated 10th November, 1906. Sickness, diarrhœa, sore throat; temperature on 10th November, p.m., 103 deg., and afterwards very variable, on several occasions being over 105 deg.; quick shallow breathing and bad cough; broncho-pneumonia. I saw the patient with Dr. Hallen, the Medical Officer of the Home, on the 21st November, as it was thought the patient was probably suffering from enteric fever. I therefore took a sample of his blood, and the following morning received a wire from the Lister Institute that the Widal reaction was negative. The patient, however, was notified as enteric fever, and removed to the South-Western Fever Hospital on the 22nd. I wrote to Dr. Caiger respecting the patient, and he informed me that a second negative Widal reaction had been obtained, and that he was of opinion it was not a case of enteric fever, but that the patient was suffering from broncho-pneumonia. (Chart shown.)

14th. C. R., male, 12 years. Admitted 17th November, 1906; patient isolated 14th November, 1906. Headache, sore throat, high temperature, and great weakness; the illness lasting about four days,

15th. E. F., female, 3 years. Admitted 13th August, 1906. Illness began 15th November, 1906. Sickness and diarrhœa, lasting about two days.

16th and 17th. K. R., female, 6 years, and G. F., female, 4 years. Both admitted 17th October, 1906. Illness began 16th November, 1906. Sickness, sore throat, feverishness, and weakness. The illness lasted three or four days.

18th and 19th. J. B., male, 8 years, and E. H., female, 11 years. Admitted 14th July, 1906, and 17th October, 1906, respectively. Illness began 17th November, 1906. Sickness and headache. Illness lasted two or three days.

20th. J. W., male 9 years. Admitted 17th October, 1906. Illness also began 17th November, 1906. Sore throat, running from eyes and nose, and slight headache. Illness lasted about four days.

The 19th patient was the one that was isolated at the Holborn Workhouse from September 29th to October 11th with headache, fever, sore-throat, and a scarlatinal rash. The second attack was very much milder.

No. of Case.	Sickness.	Headache.	Sore Throat.	Fever. Under 102°.	Fever. Over 102°.	Running from Eyes and Nose.	Rash.	Weakness.	Diarrhœa.	Length of Illness.
1	+	...	+	...	+	...	M. S.	...	...	4 weeks.
2	+	...	...	+	...	+	...	...	...	4 days.
3	+	...	...	+	...	+	...	...	...	4 days.
4	+	...	+	+	...	...	...	+	...	3 or 4 days.
5	...	...	...	—	+	+	M.	...	...	4 weeks.
6	...	+	+	...	...	...	Slight	...	..	5 days.
7	...	+	+	...	+	...	Slight	...	+	5 days.
8	...	...	+	...	+	+	...	...	...	3 days.
9	...	+	+	+	...	+	...	...	...	4 days.
10	...	+	+	+	...	...	...	+	...	4 or 5 days.
11	+	...	...	...	...	...	...	+	...	2 or 3 days.
12	...	...	+	...	+	+	...	+	...	8 days.
13	+	...	+	...	+	...	...	+	+	9 weeks.
14	...	+	+	...	+	...	...	+	...	4 days.
15	+	...	...	...	...	...	...	...	+	2 days.
16	+	...	+	+	...	...	...	+	...	3 days.
17	+	...	+	...	...	...	...	+	...	3 or 4 days.
18	+	+	...	..	...	...	...	...	...	2 days.
19	+	+	...	...	...	...	...	...	...	2 or 3 days.
20	...	+	+	...	...	+	...	...	...	4 days.
	11	8	13	6	7	7	4 Rashes	8	3	—

	Outbreak, 20 Cases.	E. Herts. Epidemic, 162 Cases.	Outbreak[1] in King Edward's Schools for Girls, Southwark, 177 Cases.
	per cent.	per cent.	per cent.
Sickness	55	52	35
Headache	40	63	98
Sore throat ...	65	60	3
Under 102° ...	30	60	In most cases above 100°, but the majority did not exceed 102°.
Fever, above 102°	35	13	
Running from eyes and nose	35	82	96
Rashes	20	37 (excluding herpes)	26 (excluding herpes).
Weakness	40	Usual	Greatly complained of.
Diarrhœa	15	4	12

[1] *British Medical Journal*, February 22nd, 1890, by Dr. H. C. Bristowe.

Various rashes have often been described as being present in influenza epidemics.

Dr. Bruce Low (*Report on the Influenza Epidemic* 1889-1890 *to the Local Government Board,* quoted by Dr. Parsons) says that "herpetic patches on the lips are not uncommon. A rash, not unlike that of German measles, was seen in some cases, principally on the posterior aspect of the limbs, there being none on the face or chest."

Dr. J. S. Bristowe (quoted in the same Report) mentions "a roseolous spotty rash, either resembling scarlet fever or urticaria, about the elbows, forearms, and fingers, knees, legs and feet, and even on the trunk."

Dr. H. C. Bristowe states that in the outbreak mentioned above, 26 per cent. of the cases had erythema or papular rashes, and about 10 per cent. of the cases had herpes labialis; and in the cases in which the rash was best marked no drugs had been given.

Dr. Symes Thompson, in his continuation of Dr. Theophilus Thompson's *History of Influenza,* mentions the occasional appearance of a measly or scarlatinaform eruption, usually followed by some desquamation: erythema or papular, disappearing on pressure; lasting one to four days. In other cases rashes appear on the second or third day on the face, cheeks, and neck, and sometimes extend to the trunk and inner aspect of the limbs. In some outbreaks a large number of cases of herpes labialis.

Dr. O. Leichstenstern, in Nothnagel's *Encyclopædia of Medicine,* in his "Article on Influenza," mentions that redness of the skin, frequently scarlatinaform or measly eruption, particularly on the face, forehead, chest and trunk, frequently also on the upper extremities, more rarely on the lower, and that the rashes are only occasionally followed by desquamation. Also, that urticaria is present in some cases, and herpes in 4 to 5 per cent of the cases.

Influenza was present in London October and November, 1906, and following months, increasing to a maximum mortality in January, 1907. The following are the numbers of deaths registered in the successive weeks: October 6th, 6; October 13th, 10; October 20, 11; October 27th, 9; November 3rd, 5; November 10th, 8; November 17th, 14; November 24th, 21; and December 1st, 43: a total of 127 in two months.

Among the total patients at five of the large London

hospitals at which particulars of both in-patients and out-patients suffering from influenza have been recorded, the number of deaths was only 9 out of 5516, or 1.6 per 1000 cases. The mortality during the epidemic was very small, and it shows that there was probably a large number of cases of influenza in London in October and November, 1906.

In Dr. Parsons's *Report on the Influenza Epidemic of* 1889-1890 *to the Local Government Board*, he states that the "bacteriology of influenza cannot yet be said to be settled." A perusal of the conflicting statements of these different observers inclines one to think that the microbe (if there be one), which is the essential cause of epidemic influenza, has not yet been discovered, and that the forms which have been identified in the sputa of patients or the lungs of fatal cases, are either accidentally present or are connected with the occurrence of secondary affections for which the attack of influenza had prepared the soil.

The discovery of the bacillus influenzæ, which appeared to cause the disease, was first announced by Pfeiffer in 1892, and was soon corroborated by numerous observers in all parts of the world. It is now well known that the influenza bacillus will grow without Haemoglobin, provided that certain other bacteria accompany it; and that bacilli, which, if not actually identical with Pfeiffer's bacillus, have the closest possible resemblance thereto, are widely distributed, and produce diseases which are constantly present.

Many observations have been made in England, France, Germany and America which have shown that in attacks which are clinically typical influenza, the bacillus influenzæ may not be forthcoming. The bacillus is still met with, but it is comparatively rare. The most usual organism to find in the sputum or nasal discharge in cases of clinical influenza nowadays is micrococcus catarrhalis; after that, pneumococci, streptococci, pseudo-diphtheria bacilli, etc.

In the epidemic simulating influenza in East Herts., which I have already mentioned, the micrococcus catarrhalis was the organism which was generally found, and on the other hand the bacillus influenzæ was rarely met with.

Many doctors and bacteriologists have considered outbreaks, and cases of disease simulating influenza, as only really influenzal, if the influenza bacillus has been isolated; and consider other cases as influenza nostras, grippe, influenzal cold, or by some other name.

In Dr. Osler's "Treatise on Medicine," he states that "Ruhemann reports 1979 cases of typical grippe between 1895 and 1902; in only 115 he demonstrated the influenza bacillus. On the other hand, Lord (in Berlin) demonstrated influenza bacilli in about 30 per cent. of 100 unselected cases of acute and chronic bronchitis. Yet, during this period, there was no epidemic of influenza in this city.

"The reports are sufficiently numerous to show that the influenza bacillus is probably constantly with us. Many observations show that it is a frequent invader of the respiratory tract in the inter-epidemic periods, and is probably responsible for many of the cases of Leichtenstern's influenza nostras. Indeed, it seems to bear a similar relation to the acute infections of the respiratory tract as other common organisms. It is still unexplained why it should stand in a different relation to the epidemics of influenza as the sole cause of the disease."

It seems at present impossible to come to a satisfactory solution of the problem; and Dr. Emery, in the special influenza number of *The Practitioner*, of last January, thus concludes his paper on the "Micro-organisms of Influenza": "The only possible solution that is entirely satisfactory is absolutely hypothetical, and unsupported by any evidence. It is that influenza is a specific disease due to a definite single cause, but that this cause is undiscovered, and perhaps unsuspected; it may be an invisible microbe, a protozoan, or some depressing 'influence' acting directly on the human constitution, and of a nature as little known as were bacteria when influenza received its name. We must assume that this factor has some peculiar action on the body, causing definite symptoms, and has in addition the power of temporarily lowering its resistance to certain organisms. If Pfeiffer's bacillus is identical with the other members of the group of hæmophilic bacteria, it is a widespread organism, and there is no difficulty in seeing how it might take advantage of this breach in the defences of the body; and the other organisms are quite commonly met with in the mouth, air, etc."

"This view of the pathology of influenza is similar to that generally held with regard to scarlet fever. In the latter disease the cause is unknown, and the local lesions and complications are due to common bacteria acting on tissues of lowered resistance."

Contribution by Dr. Hamer to the Discussion on Dr. Bond's Paper.

Influenza, when its history is traced through the centuries, is again and again the "new disease," and study of its prevalences in the last seventeen years has firmly established belief in the protean character of the malady. Special interest, therefore, attaches to any somewhat aberrant outbreak, the occurrence of which coincides in point of time with recognised prevalence of influenza.

During the past winter, London, in common with many places in this country and on the Continent, has been once again hard hit; and the possibility that a particular group of somewhat anomalous cases may really form part and parcel of the prevailing epidemic necessarily presents itself. Dr. Bond's Paper thus raises questions of far-reaching importance.

The following three instances from various parts of the world are perhaps deserving of note in this connection.

In Les Charentes, in May and June, 1906, Picardy sweat, after a twenty years' retirement from the stage of history, again broke out, attacking 6000 persons during a space of six weeks. (*Bulletin de l'Académie de Médecine*, vol. lvi, No. 35; *Lancet*, November 17th, 1906.) The brunt of the mischief was borne by the villages, towns escaping, and women suffered more than men. No "causal organism" was forthcoming, but M. Chantemesse propounded a vole and flea thesis in explanation of the outbreak; the only arguments advanced in support of this being, that the districts concerned had for two years been overrun by voles, and that the patients were much flea-bitten.

Again, the *Indian Medical Gazette* (November, 1905; March, 1906; November, 1906) gives account of the controversy which has been excited by the appearance in Calcutta of a "new disease," styled by Major Rogers "Calcutta seven days' fever." This malady closely resembles dengue, and just as closely influenza. Major Rogers wrote (November, 1905): "The cases, taken as a whole, correspond more with influenza than with any other known affection." Dr. Megaw (November, 1906) inclines, however, to favour a diagnosis of dengue, which disease, he says, prevails in Rangoon and Madras; and he asks is it not incomprehensible that there should be one type in Calcutta and another in Rangoon and Madras, "considering the intercommunication?" He finally decides, therefore, for

dengue, unless, he says, "the causal organism can be isolated, and the two diseases shown to be different." Perhaps this cautious conclusion of Dr. Megaw is not altogether unwarranted, having in view the fact that when influenza prevailed in London, in the winter of 1904-1905, a "new disease" closely resembling it, but attributable to what was then regarded as a distinct "causal organism" prevailed in East Herts.: a phenomenon, "considering the intercommunication," truly surprising.

Finally, in Beyrouth, the dengue-influenza controversy is again to the fore. Dr. H. de Brun (*Revue de Médecine*, 10 Juin, 1906) discusses the anomalous dengue of 1902 and 1904. The disease he declares to be "essentiellement une maladie polymorphe" . . . "chaque épidémie donne à l'affection une allure et des particularités cliniques qu'on ne retrouve souvent pas dans les épidémies précédentes et suivantes." He furnishes particulars concerning a group of cases, and gives temperature charts. A point of special interest is his declaration that aching of the muscles of the eyeball is a pathognomonic symptom of dengue. Dr. de Brun, it should be noted, is an opponent of the thesis that dengue and influenza are one and the same disease; but it is abundantly clear that the disease he calls dengue in Beyrouth would well pass for influenza in London. In 1904 the Beyrouth dengue was more severe than in 1902, and a case of the disease exhibiting close resemblance to enteric fever was observed by Dr. de Brun.

In Dr. Bond's outbreak no "causal organism" was discovered, and there is the same trouble as regards the epidemics of Les Charentes and Beyrouth. From the Calcutta patients "a bacillus having the character belonging to those of the colon group" is said (*Lancet*, January 5th, 1907) to have been isolated by Major Rogers. In the East Herts. outbreak of 1904-1905, the tracking of the "causal organism" was fortunately entrusted to Dr. Gordon, who conclusively disposed of the claims of both Pfeiffer's bacillus and the meningococcus, though the organism to which he awarded the palm appears, according to Dr. Arkwright (*Journal of Hygiene*, January, 1907), to abound in the normal nose in children.

Were it not for the restraining influence of the thought of "causal organisms," an impious hand might even be stretched at the present time towards Glasgow and Belfast.[1] It is

[1] The deaths from "influenza," recorded year by year since 1890, in Glasgow and Belfast yielded rates of mortality considerably lower than those of surrounding populations or of towns such as Edinburgh and Dublin. The

at least interesting to speculate as to what would have happened if the East Herts. outbreak of 1904-1905 had occurred in Belfast or Glasgow last winter. Again, what is the "causal organism" of recent London influenza? According to Dr. Emery, "in some of the most recent epidemics M. catarrhalis often occurs unmixed with other bacteria; and in the same epidemic some patients may show Pfeiffer's bacilli, some M. catarrhalis, others yet other bacilli." Finally, what will be the effect upon disease nomenclature in London, of making epidemic cerebro-spinal meningitis compulsorily notifiable?

diagnosis "influenza" is perhaps more out of fashion in Glasgow and Belfast than elsewhere; while in these cities, and indeed in other places also, there may be said to be, after the lapse of seventeen years since 1890, a condition of somewhat unstable equilibrium as regards the naming of influenza-like disorders.

Bearing in mind, then, Leichtenstern's teaching as to the anomalous type of disease presented in "trailers" of influenza, and the tendency to manifestation in such epidemics of cerebro-spinal symptoms, is there not here forthcoming an explanation of the failure of last year's "trailer," hailed generally in Europe (and notably in Paris, London, and Dublin) as "influenza," to make a mark under that name in Glasgow and Belfast? Is there not, further, reason for supposing that the said "trailer" may have accounted in part for the increased mortality in those cities recorded under the heading "Cerebro-Spinal Meningitis"?

SOME RECENT MANIFESTATIONS OF CEREBRO-SPINAL FEVER.

By A. K. CHALMERS, M.D., Medical Officer of Health of Glasgow.

(*Read: Friday, May 3rd*, 1907.)

In recent years the subject of cerebro-spinal fever has already occupied the attention of this Society on two occasions.

In 1899[1] Dr. Bruce Low reviewed the history of the prevalence of the disease, and last year (1906) Dr. Farrar[2] discussed it, with special reference to its infectivity.

Dr. Low believed there was reason for thinking that the number of deaths annually attributed to the disease did not fairly represent the numbers actually occurring; and he presented a chart which brings, I think, into striking contrast a decrease in the number of deaths attributed to cerebro-spinal fever in the decade 1881-90, with an increase in the number of those attributed to simple inflammation of the brain and membranes in the same period.

This contrast seems to me the more significant because I have been watching during recent months a change in the registered causes of deaths in precisely the opposite direction, *i.e.*, a shrinkage in the number of deaths attributed to simple meningitis (if there is such a pathological entity) coinciding with an increase in the number of those correctly, I believe, termed cerebro-spinal fever.

There is appended to Dr. Low's Paper a suggestive note by Dr. Still and Dr. Washbourn regarding the pathological relationship between basilar meningitis in children and true cerebro-spinal fever; and it would seem a not-unlikely result of the increased attention which all forms of meningeal disease are now demanding, that we shall be able, in time, to revise our nomenclature and re-classify the several forms, not only by their symptoms, but also by the organisms with which they are associated.

The question is not wholly one of scientific precision, but of every-day utility. Is cerebro-spinal fever never present except in epidemic form? Is every outbreak a re-invasion, or only the result of exalted activity and

[1] *Transactions* of the Epidemiological Society, vol. xviii, p. 53.

[2] *Ibid.*, vol. xxv, p. 245.

virulence in an organism to which for a time we have become tolerant until something occurs to disturb the balance?

Whether it is always present is a question which continued notification alone can answer; whether the disturbance is one of external conditions, or an acquired susceptibility in individuals, is at the moment one of surmise. One recalls the recurring waves of influenza and the gradually rising death-rate from pneumonia, as at least suggesting probable influences acting in this direction.

Apart from such generalisations there is unhappily ample evidence that the disease is at present widely spread; and the extent to which it is present in this country is indicated by the fact that 119 local authorities in England and Wales, and 163, representing 81 per cent. of the population of Scotland, have included it among the notifiable diseases.[1] In Ireland it is now notifiable in 6 county boroughs, and 91 Urban and Rural districts. Twelve months ago it was not notifiable anywhere, although several isolated cases, and one or two limited groups, had been observed both in England and Scotland.[2]

Outbreak in Glasgow.

The presence of the disease was recognised in Glasgow in the spring of 1906, and it is with its subsequent development that I wish chiefly to deal.

I must here claim your indulgence if I present a very imperfect picture of this. For one reason the outbreak is still in currency, and any opinion expressed is subject to revision later on. Further, I have had to prepare these notes under very considerable pressure of other work; and, indeed, my chief object is to obtain your opinion on such apparent facts as I can present.

And the better to define the subject we are to discuss, I shall quote to you a description of the disease by Dr. Grimshaw,[3] which fairly enough corresponds with what we are now witnessing, although there are some important differences which are of interest.

[1] For this information I am indebted to Mr. Power and Dr. Leslie Mackenzie, of the Local Government Boards of England and Scotland respectively, and to Surgeon-Colonel Flinn, Medical Inspector of the Local Government Board of Ireland.

[2] During the years 1874-82, no deaths were registered in Scotland as due to cerebro-spinal fever, but between 1883-1904 the cause of death was so named in 102 cases. Of these, 40 per cent. were in children under five, a much smaller proportion than in our present experience.

[3] Quain's *Dictionary of Medicine*, 1st edition, vol. 1, p. 226.

Dr. Grimshaw's description, drawn, I think, from the disease as he saw it in Dublin, is as follows:—

"An acute epidemic febrile disease, characterised by sudden invasion, with extreme nervous shock, vomiting, excessive pain referred to the back of the neck and spine, spasmodic contraction of the muscles, excessive sensibility of the spine, and frequently delirium, accompanied by *purpuric eruptions, either circumcised, raised hard, and shotty to the feel; or extensive purpuric spots or patches,*[1] *frequently accompanied by vesicular eruptions, usually of herpetic, but sometimes of a pemphigoid, character, and frequently purulent inflammation of the eyes.*"

"*Age.*—The disease usually attacks those approaching the age of puberty or in early adult life. It is not infrequent in young children."

"*Occupation.*—It appears specially to attack recruits in the Army and Royal Irish Constabulary.[2] Excessive fatigue seems to predispose to the disease."

It may here be remarked that in our present experience the rash is never hard or shotty, or, indeed, palpable to touch, and never larger than a split bean; and that fully half the number attacked are children under 10 years. Further, that while the early stages are characterised by extreme restlessness, the muscular state, later, is one rather of tonic rigidity than of intermittent spasm.

But, as bearing on the question of age incidence, I may here note that along with unmistakable evidence of increasing virulence which marked the second period of the outbreak in Glasgow, there occurred also an increase in the proportion of cases at older ages.

I have already indicated that what may be termed a pre-epidemic period occurred, and it will here be useful to indicate the clinical features of both periods. The following description was prepared for me by Dr. Dow, Senior Resident Physician in Belvidere, in September:—

Description of Clinical Features in Pre-epidemic Period.

"The patients are mostly children or young adults. The onset of the disease has been sudden, in all cases being

[1] This may correspond with the hæmorrhagic form of the disease which is described in other recent outbreaks, but we have had nothing resembling it.

[2] For reasons to be afterwards stated, it would have been interesting to know the cubic space per head allowed at that time in the Royal Irish Constabulary dormitories, but Surgeon-Colonel Flinn, after inquiry, tells me that there is no record.

ushered in with shivering, severe occipital and frontal headache, and in many cases with pain in the cervical and lumbar spine.

"*Vomiting* has been an early and almost constant distressing symptom.

"*Retraction of the head,* accompanied by painful stiffness of the muscles of the neck, has been practically a constant feature of the disease. The head may be so far drawn back that the occiput lies between the shoulder blades. In one case in the second period this over-extension reached to the nates.

"*Rigidity of the muscles of the back* is common, and in a few cases the back has been so greatly arched as to present the condition of opisthotonos.

"*Kernig's Sign* has been constantly present—viz., when the leg is raised in an extended position it suddenly becomes rigidly flexed, the flexor tendons at back of knee standing out prominently. The knee-jerks in some cases have been exaggerated, in others difficult to elicit. Plantar reflexes have been, as a rule, exaggerated. Ankle clonus has never been present. Of sensory symptoms, the most constant has been severe occipital and frontal headache, which persists from the outset throughout the disease in all the cases.

"*Great sensitiveness along the spine* and marked hyperæsthesia of the whole body has been present in many of the cases. Delirium has been usually present at onset, and sometimes of a maniacal type. It may give way to coma, or subside during the course of the disease. The pupils, as a rule, have been equal, and have responded to light, but in a few cases they are unequal, or have varied from day to day. Squinting has occasionally been observed. Nothing definite in the way of paralysis has occurred.

"The *face* has, as a rule, been flushed, suggesting pneumonia. Herpes has been common at the angles of the mouth and on the lips, and extensive herpetic eruptions have been found on the face, neck, shoulders and arms.

"A *petechial rash* has been observed, but only in a very small percentage of the cases, and has usually appeared within the first few days. The petechiæ have been found distributed all over the surface of the body, and have varied in size from the diameter of a pin-head to that of a threepenny-piece. The outline of these spots has been irregular. In one case a subcuticular mottling accompanied the petechiæ, somewhat resembling that of typhus.

"The *temperature* has been irregular and variable, but

usually of a remittent type. The pulse has often been markedly slow in adults, ranging from 40 to 50 per minute. In children the pulse has usually been rapid, and of low tension. The lungs, as a rule, have been free from lesion. Albumen has only occasionally been found in the urine. The spleen has never been found to be enlarged.

"Purulent discharges from eyes and ears have commonly occurred during the course of the disease."

Description of the Clinical Features at Later Period.[1]

Since the above description, the disease has assumed a more acute or fulminant character, many cases ending fatally within a few hours of the onset.

An acute case has these symptons:—A prodromal period lasting for an hour or two to twenty-four hours (rarely longer), during which the patient feels out of sorts, eats little, has some pains in the legs (a common prodrome), or has a mild headache and is dull; a rigor may be present or absent, and may precede by a few hours the actual onset.

The attack commences with vomiting or retching, a symptom which is never absent; or it may be preceded by a sudden pain in the head. The vomiting may be prolonged and recurrent, and the headache so severe as to at once launch the patient into wild delirium.

Next follows the irritative stage, with delirium, restlessness, nervous spasms, rigidity, screaming, frequency of micturition and vomiting, and contracted pupils. This stage may be absent or prolonged, and is followed by a comatose state, in which the patient is quiet when not disturbed; breathing becomes rapid and stertorous, face flushed and cyanotic. Death occurs in 24 to 48 hours, or longer.

Of the particular signs, stiffness of the head and Kernig's sign are the chief. The knee-jerks are active in most cases, and there is no ankle clonus. The pupils are contracted and fixed at first; later they are dilated, and fixed or sluggish. Squint is common.[2] Conjunctivitis is the rule, and the membrane is frequently hæmorrhagic. There is commonly a general spastic condition, but convulsions are

[1] Prepared by Drs. Brownlie and McGregor, Belvidere Hospital.

[2] Dr. McGregor adds that the squint is mostly spasmodic and variable, as opposed to being paralytic and fixed: a circumstance which plays an important part clinically in enabling the disease to be distinguished from tubercular meningitis. It is rare also to find optic neuritis.

rare; in some cases Jacksonian epilepsy has been present. A petechial rash[1] has been frequent, coming out a few hours from onset as a rule. It is distributed mainly on the abdomen and legs, although occasionally it is present on the face, and consists of subcuticular ragged hæmorrhages. Herpes has been more frequently present than the rash. The other features are much as formerly described.

Total Volume of Meningeal Diseases.

With the introduction or recognition of a new cause of disease it is to be expected that some displacement will occur among those which present like clinical features. And if transference results, the precise effect of the new factor can best be appreciated by considering it in relation to the total volume of deaths in the class to which it belongs. In order to illustrate this, I introduce a Table of deaths from each of the three classes of meningeal deaths, yearly numbers being given for the years 1901-6, and those for the first quarter of 1907.

Glasgow.—Meningeal Disease: Number of Deaths Registered, 1901-6, *and for first quarter,* 1907.

—	1901.	1902.	1903.	1904.	1905.	1906.	1907 (1st Quarter).
1. Cerebro - spinal Fever	1	...	...	...	...	147	312
2. Meningitis (simple), inflammation of the brain	438	414	411	388	363	329	39
3. Tubercular meningitis	237	244	240	260	237	307	105
	676	658	651	648	600	783	456

In the present instance, two most notable changes have taken place since cerebro-spinal fever was recognised. In the first place, the total volume of meningeal disease has increased, and the deaths attributed to simple meningitis have decreased. If we multiply the deaths in the first quarter of 1907 into an annual figure, those ascribed to

[1] The proportion of cases in which the rash was present varied at different periods of the outbreak, being present probably in the ratio of 1 to 5 cases during its worst period.

simple meningitis have decreased by one-half, and those attributed to tubercular meningitis have increased by a third, when compared with the figures for 1906.

This apparent increase in the number of deaths from tubercular meningitis is not supported by any other fact within my knowledge, and I think it suggests the inclusion of some which are due to cerebro-spinal fever.

But in what light are we to regard the shrinkage of simple meningitis? Has there been a transference to the cerebro-spinal fever group of many deaths which, without this disturbing factor, would still have found place under their original designation?

Meantime, until a more complete clinical picture of the symptoms which accompany each of the several forms of meningitis is forthcoming, bacterial verification alone can afford an answer, and this is not at all times possible. I have endeavoured to find one in a comparison of the morbidity rate of cases in hospital, verified and not verified bacterially, but which present similar clinical symptoms, with those similarly grouped at home, and the result for the 1906 cases may thus be stated:

Cerebro-Spinal Fever.—Cases and Deaths in Verified and Non-verified Groups.

1906.	Bacterially Verified.	Not Verified Bacterially.[1]
In fever hospitals	65	28
At home or elsewhere	22	77
	87	105
Deaths:[2]		
In fever hospitals	47	20
At home or elsewhere	18	56
	65	76

—	Bacterially Verified.	Not Bacterially Verified.
Hospital	72 per cent.	71 per cent.
Home	82 per cent.	73 per cent.

All forms of meningeal disease have, unhappily, a high morbidity rate; yet I think in the foregoing Table we

[1] These were on clinical grounds regarded as cerebro-spinal fever.

[2] *Death-Rates.*

appreciate the true significance of the "non-verified" case, and with it the validity of the argument for transferring some deaths from the class of simple meningitis to the epidemic variety. Of 105 cases belonging to the "non-verified" category, 76 died, which is equal to a fatality rate of 72 per cent.; and the proportion of fatal cases scarcely varies, whether we take it on the hospital or home cases separately. And on comparing both with the fatal cases among the bacterially verified, the fatality rate corresponds almost accurately with that of the hospital cases, but falls short of that obtaining among the "home" cases, where the fatality rate is 82 per cent.

If we accept this as indicating that cerebro-spinal fever was present before it was recognised, and that deaths due to it were still being registered as simple meningitis, we may, by following the number of deaths registered in the several months of the year, put our finger on the precise point of time when the changes which we have been indicating occurred. And for this purpose it will be sufficient to deal in detail only with the deaths occurring under five years.

Deaths Registered as due to Meningitis, Inflammation of Brain, etc. Ages, 0-5 Years.

Months.	Total Deaths, 1901-5.	Average Number Monthly.	1906.	Departures from Averages, July to December.	1907.
January	117	23	31		14
February... ...	102	20	31		6
March	124	25	20	+23	8
April	138	28	27		—
May	132	26	32		—
June	125	25	29		—
	738	147	170	+23	
July	133	27	5	−22	—
August	152	30	7	−23	—
September ...	117	23	18	− 5	—
October	114	23	14	− 9	—
November ...	98	20	8	−12	—
December ...	106	21	9	−12	—
	720	144	61	−83	
Total ...	1458	291	231	−60	

On running down the line of figures under 1906, two facts are apparent. A change, which is scarcely a natural

one, began in July. The shrinkage which then occurs has no parallel in former years. During 1901-05 the deaths occurring monthly were distributed in a fairly uniform manner throughout the year, being on an average 123 in the first six months, and 120 in the second. In 1906, on the other hand, 170 deaths are attributed to meningitis during January to June, and only 61 in July to December. The increase in the first half of the year is quite as striking as the shrinking in the latter half, but its significance differs.

Turning now to the tubercular form of meningitis, we may also note some changes.

Deaths Registered as due to Tubercular Meningitis, Ages 0-5 Years.

Months.	Total Deaths, 1901-5.	Average Number Monthly.	1906.	Departure from Average.	1907.
January ...	66	13	15	—	29
February...	74	15	13	—	24
March ...	76	15	16	—	27
April ...	95	19	14	—	—
May ...	83	17	15	—	—
June ...	62	12	12	—	—
	456	91	85	−6	—
July ...	79	16	21	+ 5	—
August ...	64	13	25	+11	—
September ...	60	12	21	+ 9	—
October ...	73	15	18	+ 3	—
November ...	56	11	21	+10	—
December ...	68	14	27	+13	—
	400	81	133	+51	—
Total ...	856	172	218	+45	—

If we take as our basis for comparison the average number of deaths occurring in each half of the years 1901-05, we find some tendency towards a decrease in the incidence of the disease during the months January to June, but an increase from July to December. This difference is shown in 85 deaths in all being recorded in the first half of 1906, as against 91 in the corresponding portion of 1901-05; while from July to December the deaths attributed to it in 1906 number 133, as against 81 in previous years.

This, I think, may be taken as indicating that early in the

year the whole volume of meningeal disease underwent an increase which was at once recognised. At first it was regarded as simple meningitis, but when attention was directed to the presence of cerebro-spinal fever, many deaths were transferred to this category, and some, I think erroneously, to tubercular disease.

It is not necessary to continue this comparison into the later ages. After 20 the deaths from meningeal disease are relatively few in number; and changes quite similar to, but more limited in extent than, those occurring under 5 were observed.

The impression, therefore, left on my mind is that we have here some evidence for regarding cerebro-spinal fever as probably a constant element among our causes of death, but one which has had its virulence increased by some cause which we are not presently acquainted with.

Distribution in Glasgow.

During 1905 I had, through the courtesy of Dr. Wallace Anderson, of Dennistoun, repeated opportunity of seeing with him several isolated cases of meningitis of a type[1] which he considers to have been present since 1891. No suggestion of grouping, however, occurred; nor were there any in which the organism was recovered, until the following incidents arrested attention:—

1. During March, 1906, two suspected cases were reported in a family residing in Main Street, Gorbals. Both were children, who sickened on the 10th and 13th respectively. The first child died after 22 hours' illness, the second after nine weeks. It was only after the disease was recognised in the children referred to in the following paragraph, that an effort was made to establish the accuracy of the diagnosis here by bacterial inquiry.

2. Meanwhile, in April, two children, aged three and eight, of a family which had recently arrived in town from Shettleston, sickened within 24 hours of each other. In the elder child death followed in four days; in the younger, after 22 days. These were the first to be verified bacterially in the Laboratory of the Public Health Department.

Coincidently with these, a male adult, who had arrived in Glasgow from Bonar Bridge on April 7th, sickened on the 15th, and died on the 19th in the Royal Infirmary. From this patient, also, the organism of Weichselbaum was recovered.

[1] Chiefly owing to the occurrence of paralytic sequelæ, such as hemiplegia, deaf-mutism, etc. (See Notes by Dr. Anderson at end hereof.)

Other cases were also intimated from the Royal and Western Infirmaries and elsewhere; and by the end of May we knew of 23 probable cases, 2 of which sickened in March, 9 in April, and 12 in May. Of these, 16 proved fatal. In 3 cases, however, although death occurred in hospital in Glasgow, the patients had been admitted from Port Glasgow, Partick, and Whifflet, so that a considerable part of the Clyde area was already involved in the outbreak. Moreover, in the preceding winter (1904) cases had been recognised in one of the Clyde watering-places, and, almost coincidently with our own, cases were reported from Lanarkshire.

In 6 the organism of Weichselbaum was recovered. One death from meningitis occurred in a soldier, but the organism present was the *Staphylococcus aureus.*

Till the end of March, 1907, the movement of the outbreak falls into two periods—not equal in length, but sharply divided by the numbers occurring, by their distribution, and by evidence of an increased virulence of attack.

The second period began in the week ending January 12th,[1] and although up till the end of 1906 only three wards in the city had an absolutely free record, quite two-thirds of the cases were from the east and north-eastern portions, which have an estimated population of 334,179, or about two-fifths of the whole. Yet in none even of these wards did the cases occur in consecutive weeks. In some, indeed, they were separated by intervals of weeks. But when the increasing prevalence was established in January, weekly recurrences became more frequent, and in this respect the outbreak assumed one at least of the features of a true zymotic disease.

The following Table presents this altered incidence. A considerable portion of the increase in the second period

Wards.	Population.	1906. (June to December.)		1907. January to March.	
		Cases.	Per cent.	Cases.	Per cent.
1—9	...	134	67.3	251	53.6
9a—26	...	65	32.7	217	46.4
Total ...		199	100.0	468	100.0

[1] The mean temperature of the week ending December 29th was low, and this was regarded as having some bearing on the increased prevalence which followed. But the meteorological associations can only be adequately considered when the outbreak is over.

was supplied from the districts in which formerly the disease had been least prevalent.

Changes Accompanying Increased Prevalence.

The first most noticeable feature which accompanied the increased prevalence of the disease was the increased severity of attack, which I have already referred to in describing its clinical features. There was also a more frequent occurrence of multiple cases in families—an increasing tendency to invade families living under better housing conditions, and a lessening in the proportion of cases in infants under one year.

There is a tendency, I think, to regard the disease as being less influenced by insanitary conditions than most others with which the sanitarian is called to deal. Inquiring with regard to this some time ago, I quote some of the notes made at the time.

In one ward, out of 25 invaded houses, 11 were definitely dirty, although not filthy in the sense of administrative action. In another of 50 invaded houses, 12 were definitely filthy. In a third, with about 60 invaded houses, in 6 only has there been any degree of dirtiness. And again, of 40 cases all were in relatively-clean houses.

The general conclusion was that the houses invaded in any district reached the average standard of cleanliness for that district.

From this method of classifying them, it was impossible to suggest that the disease was invariably selecting the dirtiest houses; but when one discarded the general term "dirtiness" for one of pressure on air space, the question took a different complexion, which may thus be indicated:

Proportion of Cases occurring in Houses of several sizes compared with Proportion of Population living in them.

—	(1.) 1906. Proportion of Cases Occurring.	(2.) Proportion of Population Living in Houses of Various Sizes. (Census, 1901.)	(3.) 1907. January to March. Proportion as in Column (1).
1-apartment	22	14	18
2 „	62	47	61
3 „	14	21	15
4 „ and upwards	2	18	6
	100	100	100

It would be possible to establish a similar excessive incidence in houses of smaller size for almost all the infectious diseases, and for some which are not infectious; but the comparison, I think, suggests that of all the conditions which may be classed as insanitary, that of which the system is least tolerant is misuse of the air of respiration. Indeed, there occurred one instance, to which I shall again refer, where, in a densely-overcrowded house, the disease exploded with an intensity which recalled typhus fever, and attacked fatally 5 out of 10 inmates. Here there was a family of 10 persons, of whom 5 were adults, living in a two-apartment house, containing just over 2,100 cubic feet.

Support to the suggestion that air impurity or defective ventilation promotes the spread of the disease is afforded if we compare the number of inmates of invaded houses with the average for each size; for in the one-apartment houses which were invaded there were more than 4 persons (4.3) as against 3.183 for all houses of this class; in the two-apartment houses which were invaded the average occupancy was 6 persons as against less than 5 (4.927) for all houses of this class; and in the three-apartment houses which were invaded the occupants averaged 6.7 against 5.409 in all houses of three apartments.

Number of Inmates in Invaded Houses compared with Average Number in all Houses of corresponding size.

Size of Houses.	Invaded Houses, 1906.	Average Occupancy. (Census, 1901.)	Invaded Houses, 1907. (January to March.)
1-apartment ...	4.3	3.183	4.1
2 ,, ...	6.0	4.927	6.1
3 ,, ...	6.7	5.409	7.4

Age-Distribution.—The age-distribution of the disease is of some importance. Dr. Grimshaw's statement is that it is common in those approaching puberty or in early adult life, although not infrequent in children. It would appear to have been mainly a disease of early adult life in several outbreaks; and from Dr. Porter's Report (1906) on the Health of Johannesburg, I find that in the recent outbreak there it attacked mainly white children and Kaffir adults, the latter being employed, I think, in certain of the mines.

There are obvious objections to comparing different out-

breaks on the basis of attacks only, but in the following Table I have adopted this method of stating the proportions given by Dr. Taves, of New York,[1] in his analysis of the Gouverneur Hospital cases, and comparing them with our own.

Percentage Age-Distribution of Cases.

—	−1.	−5.	−10	−15	−20	−25	−35	−45	−55	55+
Fiske Fund Essay ...	9	38	23	21	6	3	oldest 25 years			—
Glasgow, 1906[2] ...	18	38	20.5	10.2	4.4	3.9	2.9	.9	.9	—
Glasgow, 1907[2] (January to March)	14.5	38.1	18.2	11.6	5.5	2.8	5.5	2.8	1.7	—

Comparing both with the proportion (71 per cent.) given by Hirsch of 1267 fatal cases, New York has 91 per cent., and Glasgow 87 and 82 per cent. of cases, at ages 0-15.

The proportion of cases among infants under one year has some bearing on methods of infectivity; and here we may only note that in Glasgow we had 18 and 15 per cent. against 9 in New York.

Nature of Food in Infants under One Year with Relation to Method of Infection.—At an early period the condition of the intestine in fatal cases arrested attention by the presence of patches of congestion in the intestinal canal. These were situated sometimes in the duodenum, but most commonly towards the lower end of the ileum, where the congestion might be confined to Peyers patches, or be more uniformly distributed. Did food play any part in the spread?

One or two cases brought definitely into view the occurrence of quite temporary diarrhœal disturbances, either in the patient or in others of his family, preceding the definite onset of the disease; and this led to systematic inquiry for minor disturbances in health in the inmates of invaded houses. But no mass of evidence in this direction could be found, and efforts to recover the meningococcus from the intestinal discharges or in the bowel wall have not hitherto been successful.

But on the general question I am disposed to regard the relative infrequency of simultaneous attacks in families, and

[1] Fiske Fund Prize Essay.

[2] Subject to revision, as all cases registered as cerebro-spinal fever are included in the figures.

the occurrence of the disease in children who, after inquiry, one can regard definitely as being wholly breast-fed, as setting aside food as a common vehicle of infection—if it is indeed one which is ever operative—and of this we have no evidence.

In one or two instances of breast-fed babies, however, the occasional soiling of "dummy teats" was noted as affording a possible method of mouth infection.

I may here place on record the age and character of the feeding in the case of 43 infants, where it was carefully investigated.

Cases Occurring among Infants under One Year, and Nature of Feeding.

Age in Months.			Total.	Nature of Food.
−3	−6	−12		
2	10	12	24	On Breast alone.[1]
—	6	5	11	On Artificial Food alone—(Milk, condensed & sweet, Bread.)
—	2	6	8	On both (Porridge—Milk, condensed & sweet.)
2	18	23	43	Total.

Multiple Cases in Households.—I have already referred to one instance when the disease behaved in an overcrowded house much after the manner of typhus fever. There were others of a like—although less pronounced—form; and it rapidly attracted notice that in the second period of our outbreak these occurrences were more numerous than during 1906. It was regarded, indeed, as evidence that the organism was acquiring an increased virulence. And yet, the most striking feature of these incidents is that they are relatively infrequent. Of 186 households invaded during 1906, there were 6 only in which 2 cases occurred, and 1 family had 3 attacks. There is thus something less than 4 per cent. (3.8) of multiple attacks in this period; but during January to March, 7.5 per cent. of the invaded houses had multiple attacks, there being 26 households in which 2 cases each occurred, 3 households had 3 cases each, 1 had 4, and another 5.

It was difficult at first to find any factor which appeared to determine the greater incidence in these houses. The special susceptibility of children, as indicated by the

[1] One 20 days old; one 8 weeks old.

excessive proportion of cases at ages under 10 years, was of course obvious, and so our multiple cases usually occurred where children were numerous. But when the question of air impurity emerged, the actual number of inmates in invaded houses assumed greater importance; and it was found that an approach to grading the number of inmates in relation to the number of attacks therein could be made.

This may be indicated in the following Table.

Number of Persons Attacked per House.	Inmates per House.			
	One Apartment.	Two Apartments.	Three Apartments.	Four Apartments.
1 each	4.2	5.8	7.4	7.2
2 „	5.0	7.0	7.5	7.5
3 „	5.0	8.0	—	—
4 „	—	8.0	—	—
5 „	—	10.0	—	—

In some cases the difference in the number of inmates is small, but the figures seem to me to suggest that air impurity is related both to the question of invasion of particular households, and to the possibility of multiple attacks occurring.

In these multiple invasions, however (31 houses in all), it was found that a certain number occurred at varying intervals *after* the termination of the earlier case and disinfection of the house.

Of such there were 17; but leaving aside 3 third cases and 1 fourth case, there were 13 secondary attacks occurring after the following intervals.

Interval between Disinfection of House and Sickening of Subsequent Cases.

—	Days.							Weeks.			Month.	
	1.	2.	3.	4.	5.	6.	7.	2.	3.	4.	2.	3.
No. of Cases ...	2	1	1	1	1	—	—	3	—	—	4	—

We may accept the 6 cases sickening within 5 days as due to direct contact with the sick, and should probably include with them those who sickened in the second week. The possibility of re-invasion cannot, of course, be excluded; but in the case of 11 persons not residing in already invaded houses, there was known contact of limited duration, and in 5 of these the interval between exposure and sickening extended into the second week.

The following details of the circumstances under which this limited contact occurred, and the interval between it and sickening, were ascertained.

"Contact" Cases, excluding those among Inmates of already Invaded Houses.

Nature of Contact with Primary Case.	Interval in Days between Contact and Sickening.	Remarks.
1. Playfellow ...	6	Last contact on day of sickening of first patient.
2. Visitor ...	10 to 8	Primary case died on second day of illness.
3. Ditto	6	Visited primary patient on day of sickening.
4. Playfellow ...	2	Saw patient before sickening, and was possibly infected from same source.
5. Visitor ...	9 to 6	Visited on two occasions at interval of three days.
6. Ditto	A few hours	Visited patient in hospital on day of own sickening.
7. Ditto	11	At same school, and visited during illness.
8. Ditto	3	——
9. Ditto	2 to 1	Visited house at death of primary patient, and saw body.
10. Ditto	14 to 7	Visited several times during illness of primary patient, which lasted seven days.
11. Playfellow and visitor during illness	1	——

Some of these cases suggest that the period of incubation may be less than a day, but the occurrence of secondary cases in the second week, and more especially in the second month, after known exposure, raises broadly the query whether the infecting agent is present only in the persons of those attacked, and is not sometimes present in regions which disinfecting processes do not reach.

"Carrier" cases have been recognised in diphtheria, and in cerebro-spinal fever elsewhere they would also appear to have been demonstrated. We have succeeded only in a few instances in recovering the organism from the naso-pharynx, although the late occurrence of secondary cases suggests that some such method of transmission is much more frequently in operation.

Other factors may come into operation in determining the occurrence of multiple cases. We have seen reason for thinking that they may be related to conditions of air impurity. Dr. Farrar suggested, I think, the co-operation of the meningococcus with other organisms; and remembering the exceedingly active growth of round-cell tissue in the naso-pharynx in childhood, the special incidence of the disease in these years may be explained. But if the meningococcus acquires virulence by this co-operation, it would appear to take the form of an exalted activity, because mixed infections are rare. At Belvidere Hospital two only have been observed. In one case, Dr. Brownlie tells me the meningococcus was found in association with the tubercle bacillus, in another with a diplococcus. Moreover, in 106 examinations made by Dr. Buchanan, our bacteriologist (71 of which were by lumbar puncture after death, and 35 were autopsies), he found the meningococcus alone in 71 cases; the pneumococcus alone in 2 cases; both were present in 1 case, the tubercle bacillus in 4, and a streptococcus in 1; while in 27 the results were entirely negative.

School Associations—In thirty-eight schools, single cases only occurred; in seventeen schools, there were 2 cases each; in six schools, 3 cases each; and in four schools, 4 cases each; *i.e.*, 27 in all had multiple cases.

In only five instances did it happen that two children in the same class were attacked. In one school both children sickened on the same day; in another, the interval extended to 11 days; in a third, it was 42 days, but midway in this interval a child in another standard also sickened. In a fourth school the interval was five days; but these cases formed the second and third of a group whose dates of sickening were respectively February 4th, March 7th and 12th (two cases). In the fifth school, the interval extended from January 7th to February 23rd.

Of the four schools in each of which four cases occurred, the dates of sickening in one have already been given. Of the three others, the dates of sickening in one were, January 24th (two cases, different classes); February 19th;

March 11th; in another, January 17th, February 5th and 26th, and March 3rd; while in the third school they were respectively January 7th, February 23rd, March 2nd and 16th.

If few of these dates suggest direct transmission of the disease from one child to another, it must be remembered that, so far as we know it clinically, the onset is very sudden, and usually prevents school attendance from the beginning.

Lateral Spread.—Were the disease possessed of a high degree of infectivity at comparatively short ranges, we should expect to find not only that multiple cases in families were numerous, but that the inmates of other houses in invaded tenements were also being attacked with a fair degree of frequency. This is scarcely our experience, however, for in 23 instances only was more than one house in a tenement invaded. The intervals between these invasions were as follows:—

Intervals between Invasions of Separate Houses in same Tenements.

Intervals.	Days.							Weeks.			Months.						Total.
	1.	2.	3.	4.	5.	6.	7.	2.	3.	4.	2.	3.	4.	5.	6.	7.	
No. of instances ...	1	...	2	...	1	1	...	3	...	4	5	2	2	...	1	1	23

In addition to these, there was one instance where two houses were invaded almost simultaneously, *i.e.*, within 24 hours of each other.

Whatever view we may take of the cases occurring within an interval of not more than two weeks of each other, there would appear reasonable ground for assuming that those occurring at longer intervals than one month were due either to reinvasions, or to the propagation of the disease by cases not coming within our clinical knowledge of it, and not indeed clinically recognisable as such at the present time.

Occupation.—No special incidence occurred which need be noted. The adult cases occurred mostly among the artisan section of the population.

Fatality Rate.—In such cases of the disease as were recognised, the death-rate must be regarded as excessive. This, of itself, may suggest that modified cases occur which are not recognised; and in the classification here adopted, there is a difference amounting to 20 per cent. between the

death-rate of those where bacterial verification was possible, and of those who on clinical grounds were regarded as suffering from the disease, but where the diagnosis could not be verified in a similar manner.

I have limited the statement to those only who were treated in hospital, in order that greater accuracy in the comparison may be obtained.

Cerebro-Spinal Fever: Deaths and Death-Rates in Cases treated to a termination up to March 31st, 1907. Hospital Cases only.

—	Totals.	Verified Bacterially.	Not Bacterially Verified, but on Clinical Grounds regarded as Cerebro-Spinal Fever.
Cases	312	175	137
Deaths	230	145	85
D / R. per cent. ...	73.7	82.9	62.0

Summary.—Such, then, are some of the more outstanding features of the disease with which we are dealing, and a few words may serve to summarise them.

The outbreak consists mostly of single cases in separate households, distributed over a wide area. It occurs chiefly in children who are related to each other with regard to date of sickening, but have, as a rule, no common centre of infection which is discernible.

Under ordinary conditions, therefore, it would appear that cerebro-spinal fever is possessed of a limited range of infectivity; that it spreads, in the majority of instances, through the agency of an intermediary—like the "carrier" case in diphtheria—but that under conditions which tend to produce air impurity in confined spaces it can assume the characters of a true air-borne disease—like typhus fever or measles—and attack a considerable proportion of persons breathing the same air.

The much-debated relationship of insanitary conditions to the spread of the disease would also appear to resolve itself into a question of the condition of the air surrounding the patient: when the space is limited and the air impure, the power of direct infection is greatly intensified.[1]

[1] What appears, indeed, to be a striking illustration of the infecting power of the disease, even among persons massed together in the open, is afforded by comparing the numbers sickening in the weeks ending April 27th (during which there was an important public gathering in Glasgow and district) and May 4th with those in the preceding and following weeks. For the several weeks ending April 6th, 13th, 20th, 27th, May 4th and 11th, the numbers sickening were respectively: 35, 37, 36, 54, 44 and 23.

Secondary cases occur, but *contact-groupings* are comparatively rare. On the other hand, on a spot map *place groupings* without any other associations are suggested.

When *multiple* cases occur, the sickenings may take place almost simultaneously, or with only a day or two between them; but they may, on the other hand, be separated by an interval of weeks.

None of the medical or nursing staffs of the hospitals have contracted it, but Dr. Archibald, one of my assistants, sickened on the sixth day after visiting a house in which the disease was present, and when the smell nauseated him.

It would therefore appear that the degree of infectivity is influenced both by the susceptibility of the person exposed and by the conditions of exposure.

It may be that exalted activity of the naso-pharyngeal tissue in young children helps to determine the special incidence on them, or that the more prevalent habit of kissing children affords the medium by which the organism is transferred in them from "carrier" cases. In any case, it is suggestive that the disease is less prevalent after the age at which the activity of the naso-pharyngeal tissue ceases.

If we leave the individual, and consider the conditions surrounding him—and presumably predisposing him to infection—that of air impurity, and particularly impurity from respiration, seem to play an important, if not the most important, part.

But as neither susceptible persons nor unsuitable surroundings will originate an attack, what we have to consider is by what means the disease will reach, not only unrelated members of a community but remote rural districts.

The disease recurred in some of our houses after we had disinfected them; and carefully as the details of disinfection were scrutinised, we could find no reasonable ground for thinking that anything had escaped the process save the inmates, who were not obviously ill.

Although nasal discharges have been from time to time examined, the organism was recovered only three times (14 cases) from patients by swabs taken through the anterior nares. It was recovered, however, from the naso-pharynx of four contacts, and it is suggestive that these were inmates of the houses in which four and five cases respectively had occurred.

"Carrier" cases and spray-infection would completely

explain the method of spread, were the organism recoverable in a larger proportion of contacts.

At present, we know little of the disease clinically, except in its most malignant forms.

CLINICAL NOTES ON CEREBRO-SPINAL FEVER.

By Dr. J. WALLACE ANDERSON, Dennistoun, Glasgow.

The cases which are noted hereafter have occurred at different intervals since 1891, and their importance at the moment would seem to be due to the fact that they offer illustration of children who were attacked by cerebro-spinal fever at a time when it was not generally recognised as being present in this country.

Symptoms.—General Description.

These may be stated as fever, restlessness, vomiting (not so persistent as in the tubercular form), suddenness of onset, then convulsive seizures and tonic spasms, much intolerance of being examined or handled, even when coma is beginning. *The most striking clinical symptom is tonic spasm of the nuchal muscles, with retraction of head, which cannot be replaced without great pain.* Later, when effusion becomes established, and there is coma and Kernig's contraction, the picture is very marked.

Illustrative Cases.

Case 1.—September, 1891, J. McC., male, aged 10 months. Symptoms here were at first believed to be due to tubercular meningitis, but were much prolonged and ended in recovery. Emaciation very great. Had well-marked retraction of the head, tense fontanelle, squinting, tonic and clonic spasms, prolonged coma. Was four months more or less under treatment, but recovered completely.

Case 2.—1893, J. L., female, 14 months. Again was at first believed to suffer from tubercular meningitis, until duration of illness rendered this unlikely. Was comatose for nearly three weeks. Complete recovery.

Case 3. — 1896, M. Q., female, 7 years. Came home from school sick and vomiting, complained of great pain in the head, and was soon (same day) comatose. Had the symptoms already described, and was many weeks ill. Recovery very slow, but ultimately complete.

Case 4.—1897, C., male, 10 months. This is the first child with a record of permanent injury. He was 10 months old at time of attack; retraction of head very marked, with very tense fontanelle; coma, squinting, and Kernig's sign. Was many weeks between life and death, but got slowly better. Became deaf during attack, and has since been deaf-mute, though otherwise a bright and clever lad.

Case 5.—1898, K. M., female, 3 to 4 months. Was seized during evening; violent pain in head, required opiate to control screaming. Coma followed and continued for several days. Later had hemiplegia of right arm and leg, paresis of deglutition, inequality of pupils and feeble response to light; still later, choreic movements in the right arm developed, and which still continue, associated with much muscular wasting. Here the fontanelles were not tense, suggesting that the effusion had become sacculated. Made slow and imperfect recovery.

Case 6.—June, 1899, I. M., female. Was seized at Prestwich, Ayrshire, and in a day or two brought home to Glasgow. Symptoms vague at first, then the contractions became established. During height of illness, a deep-seated abscess in femoral region was opened under chloroform. Was long ill, but has completely recovered. Now eight years of age.

Case 7.—September to November, 1901, H. McK., 2 months, female. Had all the symptoms, convulsions, tonic spasms, coma, emaciation in marked degree. Seemed moribund and hopeless for weeks, and as if brain would never revert to normal; yet now at age of 7, there is no evidence of attack, except bad articulation.

Case 8.—June to August, 1902, A. C. B., female, 3 months. Had usual sudden onset, with well-marked symptoms, fulminant in type; early left pneumonia, with a marked consolidation. Very marked degree of muco-enteritis, with bloody stools; marked retraction of head and long-continued coma. Was very ill from June 6th to August 30th—eighty-five days—but made complete recovery.

Case 9.—J. D., male, 2 years. Symptoms began with general convulsions, necessitating the administration of chloroform. Ordinary contractions, with Kernig's sign, soon supervened. During prolonged coma he emaciated rapidly, and on recovery was discovered to be deaf.

He is now being educated at the Deaf and Dumb Institution, otherwise bright and healthy boy.

Case 10.—February, 1905, Baby Fraser, female, 7 months. Had convulsions, followed by well-marked contraction in left arm and leg. Later on, hemiplegia on other side. At time of this child's illness four others were ill in the street where she resided (two of them, living in one lane, were cousins), and one in an adjacent street. Thus there was a suggestion of place-grouping.

Case 11.—December, 1905, A. C., male, 1 year. Was seen in consultation with Dr. Lindsay Steven, who agreed as to its character. Rectal temperature ran between 104 and 105. Kernig's sign present. After temperature became normal, child weak and very nervous, shrinking from the approach of anyone. Complete recovery.

Case 12.—July, 1906, S., male. Born in 1904. Symptoms not marked at first. Child emaciated progressively; seemed almost moribund for about two months, then came slowly round, and was then found to be totally deaf.

Case 13.—1907, C., female, 4 years. Became suddenly ill, with pain in head, vomiting, and coma. Retraction of head and high fever; coma passed off in from 4 to 5 days. She seemed to be progressing, when it was observed that she was deaf. There had been no pain in head, but she was very giddy, and could not stand or walk for weeks. The striking feature in this case is that the course of the illness was short, and ended almost abortively, and yet deafness resulted.

STUDIES CONCERNING SHIP BERI-BERI.

ON POLYNEURITIS OF POULTRY (*POLYNEURITIS GALLINARUM*, EIJKMAN).

By AXEL HOLST, Professor of Hygiene of the University of Christiania, and Foreign Secretary for Norway.

(*Read: Friday, May 31st*, 1907.)

INTRODUCTION.

AMONG the diseases that have of late attracted the attention of the official medical authorities of Norway, the so-called Ship Beri-Beri occupies a prominent place. The symptoms of this disease consist, in the great majority of cases, in weakness and a pronounced dropsy of the lower limbs, extending often to other parts of the body. There also exists shortness of breath, and other symptoms of a weak heart, causing not infrequently sudden deaths from acute cardiac paralysis. But, as far as Nocht, in Hamburg, and the Norwegian Beri-Beri Committee have shown, symptoms of neuritis of the limbs are comparatively rare. For instance, Nocht was only able to show the presence of neuritis in four of his 34 beri-beri ships. Considering that neuritis is the essential symptom of the beri-beri of tropical countries and Japan, and that dropsy, though present, as a rule is not prominent in cases of this disease, it seems rather doubtful if ship beri-beri is identical with this malady. This doubt, being first emphasized by *Bullmore* and *Nocht*, seems the more obvious, because the great majority of patients suffering from the ordinary—*i.e.*, dropsical—ship disease, recover as soon as they are able to change their diet, which is not the case with the disease of the tropics and Japan.

The subject of this and the following Paper will be limited to experiments regarding the dependence of the ship disease on food; the etiology of the tropical and Japanese beri-beri being outside the scope of the present investigations.

The alleged recovery of patients suffering from dropsical ship beri-beri is ascribed to *fresh* food. This fact was chiefly

emphasized by Nocht, while the report of the Norwegian Committee already referred to contains many corresponding observations. No doubt, some cases do not, at present, fit in with this observation, a fact which may perhaps be regarded as in favour of the view that ship beri-beri may occasionally comprise more than one disease; this idea may possibly also be supported by the occurrence of neuritic cases; but in the great majority of cases, the effect of *fresh* animal food, such as meat or eggs, but, above all, of fresh, green vegetables or potatoes, is very marked. For instance, Nocht pointed out that the symptoms regularly disappear within eight to fourteen days after the patients obtain fresh food.

That ship beri-beri is very closely connected with the food is further evident from the fact that the disease all but exclusively appears on board sailing ships on long voyages. On the other hand, cases very seldom appear on board steamers on the same waters. It seems natural to explain this difference by assuming that sailing ships, on long voyages, are a long time before they reach a port, where they are able to obtain fresh provisions, whereas this is not the case with steamers.

Apart from the sore gums and hæmorrhages of the skin and muscles, which Nocht observed in the case of 12 of his 34 ships, but which the Norwegian Committee has not been able to ascertain, it seems reasonable to accept Nocht's view that ship beri-beri is a food disease, being a form of, or related to, scurvy. This opinion may also be supported by facts, quoted by Nocht, showing that cases of dropsy, without hæmorrhages or sore gums, often occur during epidemics of obvious scurvy.

Proceeding to the question what defects of the food may be able to cause ship beri-beri, I have, for lack of something better, fixed on the following facts:—

In the first place, the Norwegian sailors nearly always use, on long voyages, soft bread of an inferior quality, which is to a large extent raw and baked without yeast. Yeast, however, in Germany, has proved to be an effective remedy against scurvy.

In the second place, the sailors on long voyages are, to a large extent, compelled to use dried potatoes instead of fresh ones, because the latter do not easily keep in the tropics. Dried potatoes, however, as well as dried green vegetables, during the North-American war of rebellion, proved to be of no value as a remedy against scurvy. At the same time they are, in course of their preparation,

usually boiled in water containing some hydrochloric acid before being dried.

In the third place Norwegian sailors eat very freely of tinned food: above all much tinned meat, that is, meat that has been strongly heated. Such meat may, however, have lost some of its anti-scorbutic power, or it may even be able to produce scurvy, because strongly-heated *milk* seems to be able to produce infantile scurvy. I may also add that strongly-heated meat, as mentioned below, has been shown to produce neuritis in chickens.

But tinned food may also be of importance in another way, owing to its unpalatability. The sailors eat but little of it; their diet becomes therefore correspondingly one-sided, consisting to a large extent of farinaceous food only. I, for instance, once met a patient suffering from ship beri-beri, who told me that he and his shipmates thrice a week—that is, when they got tinned meat for dinner—only ate bread, dried potatoes, and rice.

Finally, it may be mentioned that beri-beri has often appeared on Norwegian ships in spite of a daily use of lime-juice. But, it is true, this point has not been quite cleared up: the juice may, for instance, have been adulterated.

Having regard to these possibilities as explanations of the disease, I have made a considerable number of experiments on animals. My starting-point was the interesting researches of the Dutch authors Eijkman and Grijus on so-called *Polyneuritis gallinarum*. These researches Dr. Grijus most obligingly showed me during my stay in Batavia, in 1902. About ten years ago, Eijkman found that chickens develop polyneuritis, and die when fed on "peeled rice," *i.e.*, rice-groats, only. The same occurs when they are fed on sago or tapioca. On the other hand, they do not sicken after *un*-peeled rice or after meat, boiled at 100 deg. Cent., nor do they get ill when small quantities of a special sort of bean—*Phaseolus radiatus*, in Malay "Katjang-Idjo"—is added to the peeled rice. But if these beans are boiled for two hours at 120 deg. Cent., Grijus ascertained that they lose their preventive power; the same also applies, according to Grijus, to meat, and to some extent to unpeeled rice. Finally, meat also produces the disease when boiled for some days at 100 deg. Cent.

As regards the effects of a strong heating, the experiments of Grijus have recently been repeated by Eijkman. He

found that unpeeled rye, oats, millet, and barley produce the disease when boiled for two hours at 115, 125, and 135 deg. Cent. respectively. On the other hand, he did not see any result after feeding on meat boiled for two hours at 120 deg. Cent.

There has been in the Dutch medical press a discussion, which is still proceeding, regarding the bearing of these experiments on tropical beri-beri.

It has not been my object to intervene in this discussion; but it has occurred to me that a continuation of the experiments of Eijkman and Grijus might perhaps throw some light on the possible unwholesomeness of the articles of food that I mentioned in connection with ship beri-beri; because the *Polyneuritis gallinarum*, also, is a pronounced food-disease, and a disease produced by one-sided or strongly-heated food; *i.e.*, causes that, as we saw, may also be suspected of inducing ship beri-beri. I, therefore, first made a great number of

Experiments on Pigeons.

The experiments gave the following results: When fed exclusively on "peeled" rice and water, pigeons, without exception, die on an average after three weeks, with a loss of weight of 25-50 per cent., on an average 40 per cent. As death approaches, many of the animals seem paralytic, their gait is unsteady and stumbling, and they are unable to fly; but in other cases these symptoms are less prominent.

I made thirty experiments with peeled rice. Post-mortem, there is, as a rule, a distinct but moderate œdema under the skin of the legs and feet, extending in few cases to a general anasarca.

When examined microscopically, the peripheral nerves, to a varying extent, show a typical Wallerian degeneration.

The number of degenerated fibres is greatest for the most part in the nerves of the lower limbs, where in 15 out of the 30 cases it was very great, to some extent almost astonishing. In the other 15 cases, the corresponding number was moderate or small.

As regards the question whether the disease may not be produced by other than tropical cereals, I made experiments with barley. As in the corresponding experiments on

chickens, made by Eijkman with unpeeled rice, I found that unpeeled barley is an excellent food for pigeons. But when fed on *peeled* barley, the animals as constantly die, and after the same interval as when fed on peeled rice. I made sixteen experiments with peeled barley. Seven of the animals showed a very great, nine but a moderate or small, number of degenerated fibres in the nerves of the lower limbs. I further experimented with barley-flour; these experiments gave the same results.

These results, too, agree to some extent with those of Eijkman, because he also has fed chickens on barley groats, with the result that one of his two animals got polyneuritis. The disease did not, however, develop until after an interval of several months. At the same time, he found that barley groats produce the disease much sooner when boiled for two hours at 115 deg. Cent. (two animals). As regards *pigeons*, I have not seen any difference between raw and strongly-heated barley groats.

The Norwegian sailors do not, however, eat much barley. I therefore tried with bread made of finely-sifted rye, with which no experiments on poultry have as yet been made. I fed four animals on bread baked with yeast, and four with bread baked with "Royal" baking-powder. This latter bread is not very porous, has a viscous crumb, is often badly baked, *i.e.*, to some extent raw, and so far corresponds with the bread that the Norwegian sailors to a large extent, as mentioned above, are supplied with on long voyages.

Taking a similar result for granted, I made no experiments with unpeeled rye. The Norwegian sailors do not, however, use much rye on voyages in the tropics, because they can obtain in tropical ports hardly anything but *wheat-flour*. I therefore fed pigeons on *wheat-bread*, the effect of which has not hitherto been examined. Again I fed some animals on bread baked with yeast, and others with bread baked with Royal baking-powder. Like the corresponding rye bread, the latter was not very porous, often raw, and with a viscous crumb. The result of these experiments was, that all the pigeons died, and that both sorts of bread produced in about half of the eight animals fed on each sort of bread a very pronounced neuritis; but six of the pigeons fed on bread prepared with baking-powder died in half the time of the others.

These experiments show that bread of wheat-flour, *i.e.*, the flour ordinarily used by Norwegian sailors in tropical waters, is much more injurious to pigeons than rye-bread. The experiments further show that the effect of wheat-

bread similar to the poor-quality bread used by the Norwegian sailors on long voyages was more injurious than that of bread baked with yeast. I may finally add that the latter difference cannot be ascribed to any poisonous effect of the baking-powder, because the rye-bread, prepared in the same way, did not produce the same result.

As to unpeeled wheat, peeled oats, and oat-flour, these nutriments had no effect on pigeons. I made no experiments with unpeeled oats, as I assumed that the results would be identical.

Again, pigeons died constantly when fed on *boiled potatoes*, no matter whether the fresh or dried (preserved) potatoes, mentioned above. It is true, there was some difference in so far as only one of the eleven pigeons, fed on fresh potatoes, developed neuritis, while this applied to three of six fed on dried ones. But this difference is not convincing.

Among the other experiments I made with poultry, I may finally mention some researches regarding the influence of strongly-heated beef, With this nutriment I made

Experiments on Chickens.

As mentioned above, Grijus saw chickens develop polyneuritis when fed on beef boiled for two hours at 120 deg. Cent. His experiments comprised eight animals. One chicken showed no signs of illness in spite of being thus fed for eleven months. As to four others of the animals, the result was negative, little distinct, or doubtful; one dying without degenerations after nine days, two with few degenerations in nineteen days and five months respectively, and one after nineteen days with paralysis, but without its nerves being examined. The three remaining chickens died at intervals of fourteen and fifteen days and five months; all of these animals had a great number of degenerated fibres in their peripheral nerves.

However, in these experiments the beef was more strongly heated than in the manufacture of tinned meat. For instance, according to the Paper of Bischoff and Wintgen, the meat in a German manufactory is boiled from one and a-quarter to two hours at 100 deg., and afterwards only for one hour at 120 deg. Cent. The same duration of the boiling is also indicated in the *Calender für Conserveindustrie*, 1905. It may, too, be objected that the experiments of Grijus are made with meat from the

special oxen that exist in Java ("Karbouwen"); this meat does not, for instance, taste quite as our beef. It may also be added that Eijkman, as we have seen, did not observe any result after feeding on meat boiled for two hours at 120 deg. Cent. However, his experiments did not comprise more than three animals, and were made with *horse* beef. Two animals died with a considerable loss of weight, but without neuritis, after one and four months respectively. The third animal appeared, after four months, healthy.

I have experimented with ox beef that had been boiled less intensely, and with this I made two series of observations, each comprising four chickens. In the first series, two animals were given beef, boiled for half an hour at 100 deg. Cent., and for one hour at 120 deg. Cent.; two control chickens got the same beef, boiled for half an hour at 100 deg. Cent. All boiling was done in an ordinary autoclave —the beef was always minced, and was found to be thoroughly boiled.

The result of this experiment was that all animals, little by little, ceased eating, and lost considerably in weight. On the seventy-ninth day one of the 100 deg. animals died, and one of the 120 deg. animals was killed as a control. On the eighty-ninth day the surviving 120 deg. animal died, and on the ninety-sixth day the surviving 100 deg. animal was killed as a control.

All animals were very emaciated. At first sight it seemed that the result of the experiment was quite negative—that is, that there was no difference between the two pairs of animals. But, as a matter of fact, the difference was very great indeed. In the first place, both 120 deg. animals showed a very marked subcutaneous œdema, which did not appear in the two other chickens. In the second place, there was found in the two first-mentioned animals a very extensive polyneuritis, while the examination of the two 100 deg. animals was, in this respect, too, negative.

In the second experiment, two chickens were given meat, boiled for half an hour at 110 deg. Cent.; two other animals received in this experiment the same meat, boiled for half an hour at 100 deg. Cent. This time all animals ate well, and increased in weight. On the forty-ninth day one of the former animals suddenly got paralysed and died with an extensive neuritis. The remaining three animals continued to increase in weight, and were killed on

the sixty-eighth day. None of them seemed ill at the post-mortem; but microscopically the surviving 110 deg. animal, but none of the 100 deg. chickens, showed a moderate neuritis.

It therefore seems evident that beef is able to produce polyneuritis in chickens, even when boiled at a lower temperature than the 120 deg. Cent. usually reached in the manufacture of tinned meat.

I may add that I also made several experiments in order to ascertain whether the polyneuritis described may be due to a simple starvation. For this purpose I fed twelve pigeons on 5-10 grams of peas or unpeeled barley a day, with the result that they died after five to seven weeks. None of them, however, showed any neuritis. These results agree with those of corresponding experiments made by Eijkman. The polyneuritis described above must therefore be considered as due to a special injurious effect of the nutriments supplied.

Before leaving the experiments on chickens, it may be added that the beef had always recently been boiled. That is to say, the effect of the strongly-heated beef can only be ascribed to a decomposition of one or more constituents of the beef produced by the high temperature or high steam-pressure used in the boiling.

The foregoing experiments may need to be supplemented in various directions. For instance, I twice saw polyneuritis occur in poultry yards in Norway. But I was not able to ascertain to what food the disease was to be ascribed. I only know that in one of the cases, where thirty out of about two hundred chickens had died, the mortality ceased at once as soon as the food was altered.

A further pursuit of the experiments of Eijkman and Grijus may also be of interest, on account of the additional light they may throw upon the deterioration of food by strong heating. This point is of interest, not only as regards the nutritive value of tinned food, but also in reference to the steam-boiling of different articles of food used in modern hospitals; because the latter is often carried out at an over-pressure of half atmosphere, *i.e.*, a temperature of about 110 deg. Cent., which temperature when applied for half an hour, has within our experience produced alteration of the nutritive elements of beef.

Moreover, several chemical questions arise. For instance —what are, properly speaking, the alterations of meat, produced by strong heating? Considering, for instance, the

fact that the *Polyneuritis gallinarum* seems mostly due to farinaceous food, is it permissible to put forward the hypothesis that the high temperature or the steam pressure produce a dissociation of the carbo-hydrates that, according to modern chemistry, form a constituent of the molecule albumen? But, with regard to chemistry, the question above all arises—what nutritive elements are absent when the malady appears? Because Eijkman has found that an aqueous extract of the outer layers of the rice-corn—that is, of rice-bran—is able to prevent the malady.

I abstain, however, for the present, from trying to answer these and other questions concerning *Polyneuritis gallinarum*, because the experiments mentioned above are unable to throw any unmistakable light upon the problem which has, from my point of view, been the principal one, viz., the etiology of ship beri-beri. It is true that the experiments described have shown that there are more of the ordinary articles of food that produce *Polyneuritis gallinarum* than appears from the Papers of Eijkman and Grijus. The experiments may also support the idea, mentioned above, with regard to the injurious effects of tinned meat and bread of inferior quality, used on long voyages. On the other hand, the experiments are unable to establish, in any convincing way, the injurious effect of dried potatoes, though this nutriment, to judge from facts, often seems connected with the malady. It may further be added that the *Polyneuritis gallinarum* much more resembles the tropical and Japanese than the ship disease, showing much oftener neuritis than ship beri-beri. And, finally, supposing that a modified feeding of chickens or pigeons produced a disease more like ship beri-beri, the objection would be that we cannot, from experiments on poultry, draw any convincing conclusion concerning man, seeing that the physiology of poultry is quite different from that of human beings.

I therefore abstained from experiments on poultry, and undertook investigations on mammalia. Some of these investigations, I will, in connection with Dr. Frölich, discuss in the following Paper.

STUDIES CONCERNING SHIP BERI-BERI.

ON THE ETIOLOGY OF SCURVY.

By AXEL HOLST, M.D., Professor of Hygiene; and
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(*Read: Friday, May 31st*, 1907.)

1. *On the Macroscopical Alterations to be seen in Guinea-pigs which were Fed Exclusively on Unpeeled Grain, Groats, or Bread.*

By experimenting with the "one-sided" diets mentioned by one of us in the foregoing Paper, we found that guinea-pigs also contract a disease, and that this disease is accompanied by very characteristic changes.

These alterations, however, do not as a rule develop until from about three to four weeks after the beginning of the experiment. The present section of our article, therefore, only concerns the sixty-five animals that lived eighteen days or more, and, in addition, one animal that lived fifteen days. These sixty-five animals had an average weight of from 300 to 500 grams. Four were fed on unpeeled oats, four on unpeeled rye, four on unpeeled wheat, seven on unpeeled barley, nine on peeled oats, thirteen on peeled barley, ten on rye-bread baked with yeast, four on rye-bread baked with baking-powder, two on a mixture of unpeeled oats and rye-bread baked with yeast, six on wheat-bread baked with yeast, and two on the same bread baked with baking-powder.

All these animals invariably died, no matter whether the grains were ground or not. On an average, death occurred after thirty days.

Moreover, these experiments afforded in other respects quite different results to those obtained with pigeons.

In the first place, the majority of the guinea-pigs exhibited, at the post-mortem, *pronounced hæmorrhages.* The latter appeared most frequently in the muscles of the hind limbs. In the legs they were, as a rule, found in the upper part of the peroneal muscles; in the deeper layers they could often be traced to the periosteal tissue around

the epiphyseal lines of tibia and fibula. At the same time hæmorrhages appeared more or less around the junctions between the ribs and their cartilages, in almost all cases that were examined in this direction. The same observation applies to hæmorrhages in the deeper muscular layers, and in the periosteal tissue at the inside of the lower jaw. Finally, there appeared, in several cases, hæmorrhages in the muscles of the fore-limbs, of the back, and of the abdomen.

In addition to these muscular hæmorrhages, there were often observed subcutaneous hæmorrhages. These also appeared, as a rule, on the hind limbs.

In all we noted hæmorrhages of the kinds mentioned in fifty-one (or about 80 per cent.) of our sixty-five animals.

We further observed *petechiæ* in the skin. With one exception, however, they were to be found only in the follicles of the vibrissæ of the lips and muscles. Here they seemed to be constant.

We have also rather frequently seen hæmorrhages from the mucous membranes of the stomach, and in the peritoneal cover of duodenum; in some cases also in the kidneys, liver and lungs. In addition to the hæmorrhages there sometimes occurred a subcutaneous œdema. This, however, was not frequent, and was nearly always limited in extent.

We also found, at the post-mortem, a *pronounced fragility of the bones.* This remark applies in several instances to the tubular bones; and repeatedly when removed from the body, the upper epiphyses of one or even both ossa humeri or tibia, or the lower epiphyses of one or both ossa femoris, separated from the corresponding shafts. As will be shown in the next section of this article, we have in numerous other cases, where no macroscopical alterations of this nature took place, found microscopically smaller or larger fissures passing horizontally through the shafts just below the epiphyseal lines, but without laceration of the periosteum. We have therefore concluded that the macroscopical separations between the epiphyses and the shafts existed *intra vitum,* but that the intact periosteum kept the fractured bones *in situ.* On several occasions we were able to prove the correctness of this view at the post-mortem, for after removing the periosteum it was sometimes easy to observe that the epiphyseal ends of the *ribs* were fractured and separated from their cartilages, in correspondence with the hæmorrhages in these localities, as described above. In one instance we

also found, after a careful preparation of both tibiæ, that the upper epiphyses of these bones lay movable on the top of the shafts, and were only connected with the latter by the periosteum.

These fractures of the long bones were due to an atrophy of the bone substance, which was chiefly pronounced in the ends of the shafts. There the cortical substance was thinner and the osseous trabeculæ of the spongeoid substance more rarefied, than was the case with control animals. This was particularly noticeable when cutting through the upper ends of tibiæ.

A pronounced fragility was also repeatedly observed in the lower maxilla; this bone sometimes actually crumbled under the fingers. This bone, too, often showed defects of the osseous substance. As a rule, the defects appeared on the outer surface of the bone. The largest were of the size of hemp-seeds. They were conjunctive with the root-tips of the molar teeth; and corresponding to the latter we also frequently observed, in the upper jaw, defects in the bone at the base of autrum Highmori.

Not only where these defects were pronounced, but in all 34 cases examined in this direction, we further found, *without a single exception, more or less looseness of the molar teeth.* Usually, most of the molars were affected; more rarely only one or two were loose. In some instances they could with ease be removed by the fingers; and in pronounced cases, after a careful preparation, a gap between the teeth and the walls of their alveoles might be observed. In other words, the latter had become too wide for the teeth.

On the contrary, we have in only a few instances found the incisors loose. The reason probably is that the incisors have long curved roots, and therefore do not so easily loose their hold.

As regards the teeth, we may add that they nearly always had a somewhat grey-greenish colour. Sometimes there also appeared diffuse bleedings in the pulp.

Finally, we may mention that the gums, too, often possessed a somewhat greenish-grey tinge. In twelve—that is, 18 per cent.—of our sixty-five animals, we noted that the gums were conspicuously hyperæmic, and sometimes swollen. However, this remark applies only to the gums on the front of the lower—in a few cases of the upper—incisors. Occasionally we found macroscopical hæmorrhages under the mucous membrane of the gums.

(As regards the microscopical observations, see the next section.) We have, however, never been able to detect ulceration of the gums.

It will be seen, therefore, that the principal points of the observations described above were (1) *hæmorrhages;* (2) a certain *fragility of the bones,* sometimes connected with demonstrable *intra vitum* fractures at the ends of the shafts and ribs; (3) *loose teeth,* connected in several cases with a marked hyperæmia of the gums on the front of the incisors, and also in some instances with macroscopical hæmorrhages under the mucous membrane of the gums.

From these observations we were led to assume that the disease might possibly be *scurvy.* It is true we only noted a marked hyperæmia of the gums in 18 per cent. of our animals. Yet, in cases of human scurvy we do not always find affected gums. For instance, more than one-half of 225 cases observed by Dr. Berthenson in St. Petersburg did not show any affection of the gums.

With regard to the fragility of the bones, several of the older writers point out that this is a symptom of frequent occurrence in human scurvy. Among other authors we refer to Gideon Harvey (1675), and subjoin the following quotations of the German observer Hoffmann: "In scurvy, all bones show a great fragility. It is astonishing to hear that patients suffering from this disease have fractured an arm when lifting it in order to remove something, or a leg when walking. Recently we observed at Münster a scorbutic patient who fractured his leg by moving in his bed." We may mention, further, the oft-quoted remarks of Poupart, who found at post-mortems of all scorbutic patients below the age of eighteen some separations of the epiphyses from the shafts. In some cases he also found fractures of the ribs at their connection with the cartilages. The same fractures have been particularly mentioned subsequently by numerous German and other authors, who at the same time found the fractures surrounded by hæmorrhages.

The same alterations apply also to Barlow's disease, that is to say, scurvy in small children. As Barlow himself has pointed out in his excellent Papers, and as this has afterwards been demonstrated by numerous other observers, this form of scurvy is also accompanied by the same separations of shafts and epiphyses, and by the same fragility of the bones, which we have previously described. For instance, in this disease there also regularly appear

hæmorrhages around the foremost ends of the ribs, which, after removal of the periosteum, are found to a large extent to be separated from their cartilages. We may also observe that Barlow, and subsequently other authors, found a universal rarefaction of the bone substance. There are also affections of the gums relative to the stage of dentition, and there are periosteal, muscular, and subcutaneous hæmorrhages. On the other hand, hæmorrhages in the skin itself, so regularly to be met with in ordinary scurvy, are often comparatively rare in Barlow's disease. For instance, of the 31 cases which Barlow had collected in 1883, only *three* showed such hæmorrhages. In so far, the disease of our animals agrees more with infantile scurvy than with scurvy in adults.

2. *On the Microscopical Alterations in the Structure of Guinea-pigs fed on Unpeeled Grains, Groats, or Bread.*

We have examined the *nerves* of many of the animals mentioned in the foregoing sections, but we have only twice been able to detect a pronounced polyneuritis. We have further, in very many cases, examined the *muscles* of the limbs; their fibres were, to a large extent, more or less degenerated.

In particular, we have submitted the *osseous system* of our animals to an extensive microscopical examination, because numerous microscopical researches have proved that *infantile scurvy* presents absolutely specific alterations of the bones.

These latter investigations are due to numerous German pathologists (Fischer, Nägeli, Jacobsthal, Schödel and Nauwerck, Schmorl, E. Fränkel, and others) Their researches have given the unanimous result—a result that constitutes a law—that infantile scurvy is chiefly accompanied by the following alterations of the bones:

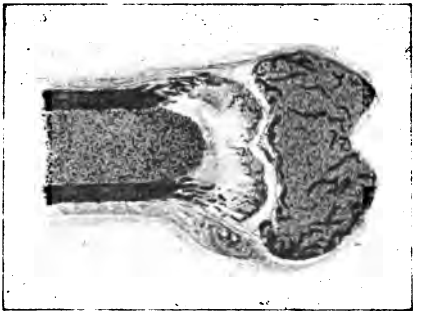
(1) *The bone-marrow* loses, in quite definite localities, its lymphoid cells. The latter are replaced by a reticular or fibrillated—sometimes also a homogeneous—tissue, containing only a few or no osteoblasts and marrow cells; instead of the latter there appear spindle-shaped or stellated cells. As regards the blood-vessels, their number, too, is considerably reduced. In this tissue, there appear often, but not always, fresh hæmorrhages or blood-pigment. Because this marrow is poor in cells, it does not, for instance, stain as well, by means of hæmalum, as the normal one; in

stained sections, therefore, it can often be distinguished, by means of the naked eye, from the normal marrow by its palish colour ("*Helles-Mark*" of the Germans; see the figure below).

This reticular, fibrillated, or homogeneous tissue is considered by the German pathologists as the remaining unchanged, or somewhat altered, reticular ground or "supporting" substance of the original lymphoid marrow; they therefore often call it "frame-work" = or "supporting marrow" ("Gerüst-" or "Stütz-Mark"; Schödel and Nauwerck).

These alterations appear in more or less numerous tubular bones or ribs, being *limited to the zones of the endochondral ossification*, that is, to the ossification nuclei of the epiphyses, but *especially to the ends of the shafts*. Here the "Gerüst-Mark" is intercalated as a layer of varying thickness *between the intermediary cartilages or—as regards the ribs—between the cartilages of the latter and the normal marrow of the bone*. (See the figure below.)

Finally it may be mentioned that the same diseased marrow is often to be found in the Haverian channels.



Section of the lower end of a femur from a guinea-pig fed on oaten groats. A rather thick layer, "Helles-Mark" ("Gerüst-Mark"), between the intermediary cartilage and the normal marrow of the shaft. The cortical substance of the end of the shaft very atrophied; the bone-trabeculæ of the spongeoid substance are, in this locality, almost completely wanting.

(2) There appears a *defective formation of bone with a defective apposition* on that already formed, which atrophies and is successively absorbed. These alterations, too, appear particularly in the ends of the shafts of the tubular bones and in the foremost ends of the ribs. This atrophy results in a pronounced rarefaction of the osseous trabeculæ; while

the remaining ones become irregular or slender, or appear, in microscopical sections, as isolated islets without any connection with the intermediary cartilages (or the rib cartilages). With respect to the cortical substance, this, too, becomes, in the same ends of the shafts, markedly reticent; in places there is no cortical substance to be seen at all.

As the result of these alterations the bones become fragile, which fragility chiefly affects the ends of the shafts of the long bones just beneath the intermediate cartilages, or—as regards the ribs—at their foremost ends.

These alterations of the bones have also been found in two scorbutic patients of the age of seven and fourteen (Looser and E. Fränkel). Being under the impression that the Russian medical literature might contain publications bearing on this subject, we wrote to Professor Mojssejew, in St. Petersburg. He was kind enough to reply that Dr. Krivoncha had examined, in 1888, the bones from six cases of scurvy in adults. He had found, in the tubular bones and ribs, a reticular tissue, between the meshes of which there was shown lymphatic elements, red blood-corpuscles, and blood-pigment. Though it does not appear if these precise alterations were found in the ends of the shafts and the ribs, their congruence with those mentioned above is very conspicuous indeed, when we add the researches of Uskov, who also found, by microscopical examination of cases of ordinary scurvy, a marked absorption of the bone substance (he did not describe the marrow). We therefore assume scurvy in children and adults to be accompanied by the same alterations of the osseous system.

Turning to speak of the researches concerning *our guinea-pigs*, we have examined more or less numerous bones from forty-four of the sixty-five animals mentioned in the foregoing section, and *we have found exactly the same alterations of the bone-marrow and the solid bone-substance as described above.* That is, the lymphoid marrow was in the ends of the shafts of more or less numerous ribs and tubular bones replaced by a fibrillated or reticular layer of *Gerüst-Mark*, with or without hæmorrhages, which was intercalated between the intermediary or rib-cartilages and the normal marrow of the shafts or ribs. In these localities, also, the cortical substance, as well as the bone-trabeculæ of the spongeoid substance, were atro-

phied or completely wanting. It is also worth mentioning that there appeared, in numerous cases, smaller or larger microscopical fissures passing horizontally through the shafts just below the intermediate cartilages, but without laceration of the periosteum.

How extensive this alteration often was may be seen from the figure (p. 160), showing an enlarged section of a femur from a guinea-pig fed on oaten groats. The section was stained by hæmalum, but is designed with Chinese ink.

A summary of our microscopical results is given in the Table on pp. 163 and 164.

According to this Table, we have only failed to detect scorbutic alteration of the bone-marrow in three animals. As regards two of the latter, we only examined one tibia; one of these animals was fed on rye-bread baked with yeast, the other on rye-bread baked with baking-powder. The third of these animals was fed on oaten groats; in this case we did not detect any scorbutic affection, either of the marrow of two ribs or of tibia, femur, or humerus.

On the other hand, the specific alterations appeared in more or less numerous bones of all the remaining forty-one animals. In 29 of these cases we examined the ribs; only one of these guinea-pigs gave a negative result. One or—some few times—two ossa tibiæ were examined in 40 of the 41 cases; thirty-three of these animals showed a positive result. Finally we examined ossa femoris from thirty-three and ossa humeri from nineteen of the forty-one animals, with a positive result in 20 (21 ?) and 11 cases respectively. On the other hand, corresponding alterations were hardly ever to be found in the epiphyses. Only once we observed, in the upper epiphyses of a tibia, a slight indication of this affection. The reason is this: that the epiphyses do not, as far as guinea-pigs are concerned, contain any ossification nuclei except in very young animals.

As regards the *teeth*, we have, by microscopical examination, regularly found hæmorrhages under the mucous membrane between the molars. We have further repeatedly found blood in the *free* spaces between the latter teeth, as well as hæmorrhages in the periosteum and bone substance at the base and walls of the alveoles.

—		Ribs.			Tibia.			Femur.			Humerus.		
Nutriment.	Died after	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in
	Days												
Unpeeled oats	22	5	5	...	2	2	...	2	2	...	2	2	—
	25	5	5	...	2	2	...	2	2	...	1	1	—
	28	3	3	...	1	1	...	1	...	1	1	...	1
	28	3	3	...	2	2	...	2	...	2	1	1	—
Unpeeled rye	25	4	4	...	1	...	1	1	...	1	—	—	—
	28	3	3	...	2	...	2	1	...	1	1	...	1
	25	2	2	...	1	1	...	1	1	...	1	1	—
	24	2	2	...	1	1	...	1	1	—	—	—	—
Unpeeled wheat	27	1	1	...	1	1	...	1	1	...	1	1	—
	26	3	2	1	1	...	1	1	...	1	—	—	—
	29	3	3	...	1	1	...	1	1	...	1	1	—
	25	2	1	1 ?	1	1	...	1	1	..	1	1	—
Unpeeled barley	26	3	3	...	1	1	...	1	1	...	1	1	—
	27	...	...	...	1	1	...	...	...	...	1	1	—
	26	4	3	1	—	—	—	—	—	—	—	—	—
Oaten groats	29	2	2	...	1	1	...	1	1	—	—	—	—
	31	2	2	...	1	1	...	1	1	—	—	—	—
	29	2	2	...	1	1	...	1	1	—	—	—	—
	33	...	...	...	1	1	...	1	1	—	—	—	—
	29	2	2	...	1	1	...	1	1	—	—	—	—
	28	2	2	...	1	1	...	1	?	—	—	—	—
	31	2	2	...	1	1	...	1	1	—	—	—	—
	29	2	...	2	1	1	...	1	1	—	—	—	—
	24	2	...	2	1	...	1	1	...	1	1	—	—

—		Ribs.			Tibia.			Femur.			Humerus.		
Nutriment.	Died after	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in	Examined Bones.	Typical Scorbutic Alterations in	Normal Marrow in
	Days												
Barley groats	29	...	...	...	1	1	...	...	...	...	1	1	—
	29	...	...	...	1	..	1	...	...	...	1	1	—
Rye-bread, baked with yeast	21	...	...	...	1	1	...	1	1	—	—	—	—
	31	...	...	...	1	1	...	1	1	...	1	...	1
	31	2	2	...	1	1	...	1	1	—	—	—	—
	34	...	...	...	1	1	—	—	—	—	—	—	—
	34	...	...	...	1	1	—	—	—	—	—	—	—
	46	...	...	...	1	...	1	—	—	—	—	—	—
	31	1	1	..	1	...	1	1	...	1	1	...	1
	33	2	2	.	1	1	...	1	...	1	.	—	—
	15	6	3	3	1	1	...	1	...	1	1	...	1
Do., baked with baking-powder	34	...	...	...	1	1	—	—	—	—	—	—	—
	37	...	...	...	1	1	—	—	—	—	—	—	—
	33	...	...	...	1	...	1	—	—	—	—	—	—
Wheat-bread, baked with yeast	31	2	2	...	1	...	1	1	...	1	—	—	—
	32	2	2	...	1		1	1	.	1	—	—	—
	25	...	..	...	1	1	...	1	1	—	—	—	—
	23	...	...	...	1	1	...	1	...	1	1	...	1
Rye-bread (yeast) and oats	29	3	3	...	1	1	...	1	1	—	—	—	—
	27	4	4	...	1	1	...	1	...	1	1	...	1

3. *On the Alterations seen in Guinea-pigs which Die of Starvation, or of the Effects of Feeding on Cabbage, Fresh or Dried Potatoes.*

We have seen in the foregoing section that guinea-pigs fed on different sorts of unpeeled grains, groats, or bread also get the same microscopical alterations of the bones which are found, by numerous German pathologists, to be the *essential* alteration in Barlow's disease, and *which do not,* according to the same authors, *occur in any* other malady. In the present section of our article we shall deal with experiments regarding the question whether these alterations are due to the injurious effect of some special nutriments or not.

In the first place, we have examined the effect of a *simple starvation.* Two guinea-pigs only got water, while three others daily received 40 to 60 grams of fresh cabbage each. (Otherwise they eat, when fed on cabbage only, between 100 to 200 grams a day.) The first-named animals died after a few days, the last ones after ten to twelve days. There were no loose teeth and no hæmorrhages, except some petechiæ in the follicles of the vibrissæ. On the other hand, all animals showed a pronounced universal anasarca, while the marrow of more or less ribs and tubular bones showed the alteration which is so often, under the name of "gelatinous marrow," found in human cases where death is due to wasting diseases. That is to say, the number of the lymphoid cells had greatly and equally decreased, not only in the ends of the shafts, but also, and to the same extent, in their central parts, as well as in the epiphyses, that is, in the localities which are, as we have seen in the foregoing section, not affected in the guinea-pigs described above. This "starvation-marrow," which we will, for the sake of brevity, call this affection, has already been described in starved animals by Neumann. It never shows any hæmorrhages at all.

These results might have been anticipated, because there does not appear any symptom of scurvy in *human* diseases causing an ordinary starvation (cancer oesofagi, ventriculi, etc.).

(We have nearly always found a starvation-marrow without any hæmorrhages in the animals which we have fed on *rice-groats.* They died, as a rule, within two weeks. Notwithstanding, three of these animals, two showed a very pronounced typical *scorbutic marrow.* Two of them

died after eight days, the third after twenty-two days; the latter showed also loose teeth, but no hæmorrhages.)

We have further fed seven animals exclusively on as much *fresh cabbage* as they would eat, while eleven others were fed on *boiled fresh potatoes* only. All these guinea-pigs died after two to six months, with the usual petechiæ in the follicles of the vibrissæ; but there were no hæmorrhages anywhere else, and all teeth were tight and shining white. The marrow of the bones was in some cases normal; in other cases it was a very pronounced *starvation-marrow*, without any hæmorrhages.

Consequently, it is evident that scurvy can *not* be caused in guinea-pigs, either by a simple starvation or by a one-sided diet of *any* kind. On the contrary, *the disease originates in these animals, as well as in man, as a result only of some special nutriment.*

The correctness of this view is further supported by the fact that *dried potatoes again produce scurvy.* We have seen, in the foregoing article, that the experiments on *pigeons* did not show any convincing difference between fresh and *dried* potatoes. Not so as regards guinea-pigs. We fed ten animals on the latter. The potatoes being bought from a ship-chandler, were first soaked and afterwards boiled for half an hour at 100 deg. Cent.; six of the animals died within a fortnight without particular alterations. The remaining four guinea-pigs died after fifteen, twenty, twenty-two, and twenty-six days, the first one without, the three latter *with* loose molar teeth. All four animals showed hæmorrhages round some of the foremost ends of the ribs, the marrow of which was affected in the usual scorbutic way. (The tubular bones, however, showed a normal or a "starvation-marrow.") In the longest-living animal there also appeared extensive hæmorrhages in the musculation of the thighs and of the axillas; there also was some hyperæmia on the front of the lower incisors.[1]

These results, consequently, seem able to support the working hypothesis, discussed by one of us in the foregoing article: *that dried potatoes*, too, *may be of importance in respect of the etiology of ship beri-beri.*

[1] We may add that we have repeatedly found the same typical scorbutic alterations in the marrow of tibiæ, feeding guinea-pigs on 5 grams of cabbage, boiled for half an hour at 110 deg. Cent., in addition to dried potatoes, as described above. The addition of cabbage prolongs, to some extent, the life of the animals.

4. *On the Effects of s. c. "Anti-scorbutic" Nutriments on Scurvy of Guinea-pigs.*

In several experiments we fed guinea-pigs on oats, bread, or rice, mixed with various sorts of the nutriments known in human pathology under the name of "*anti-scorbutica.*" Of the latter we have used freshly-expressed lemon juice, fresh apples, boiled fresh potatoes, and fresh cabbage.

As for *lemon-juice,* it was in three cases mixed with oats; these animals lived for from thirty to forty-eight days. Usually, however, the juice was mixed with ordinary rye or wheat bread. Of these "bread-animals," many died within a fortnight. Three animals, fed on rye-bread, lived for from thirty to thirty-four days, and three, fed on wheat-bread, for from nineteen to forty-three days.

Each animal received, in these experiments, juice from $\frac{1}{9}$, $\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{2}$ lemon a day.

As regards *fresh apples,* four animals received rye-bread and 30 grams, that is to say, about $\frac{1}{4}$ of our apples, daily. Three of these animals died after thirty-nine, fifty-one, and fifty-two days respectively; the fourth guinea-pig is still living, that is, after eighty days.

Four animals got *rye-bread* and boiled fresh potatoes in the proportion 5, 4, or 1.1. They died after twenty-three, thirty-six, forty-eight, and sixty-three days respectively.

Each of four animals received *wheat-bread* and 10 grams of *fresh cabbage* a day. They died after 46, 85, 109, and 113 days respectively. Each of four others got wheat bread and 15 grams of fresh cabbage daily. They died after 8, 33, 43, and 105 days respectively, the two former of pneumonia.

Apart from several of the animals fed on cabbage and one of the guinea-pigs fed on apples, as well as one fed on potatoes, these results were in so far unsatisfactory, as the addition of the anti-scorbutic nutriments was not sufficient to prolong the life of the guinea-pigs; and this in spite of the fact that they received large quantities of lemon-juice and apples. On the other hand, however, the *effect of these nutriments as remedies against the specific scorbutic affections was very conspicuous indeed*; because, as regards the *teeth,* these were in several cases quite fast; and apart from the animals fed on oats, the teeth showed in all other cases only a very slight indication of looseness, and were always shining white. As regards *hæmorrhages,* these appeared

only in four cases around the ribs, and in one case (oats) in the musculation of the limbs or the trunk. As for the *marrow* in the *ribs*, it was in some cases normal in all bones examined, while in other cases only one of four to seven ribs showed any scorbutic alterations. *Finally, the marrow of humerus, femur, and tibia was always examined and found normal in all the animals mentioned above.*

It may be added that many, but by no means all, of these animals showed a marked subcutaneous œdema. We have not, however, been able to ascertain any neuritis.

We further examined the effect of *a strong heating on the anti-scorbutic power of cabbage.* Each of nine animals received wheat bread, and got in addition 30 grams of cabbage daily. Three animals received cabbage which had been boiled for half an hour at 110 deg. Cent.; three, cabbage boiled for half an hour at 100 deg. Cent.; while the remaining three guinea-pigs got fresh cabbage.

The first three animals died after 47, 115, and 125 days respectively. The first of these guinea-pigs had fast teeth, and did not show any hæmorrhages, while these symptoms were very marked in the second and third animals. *All three guinea-pigs showed the usual scorbutic alterations in all ribs examined, as well as in the tubular bones.*

The 100 *deg. animals* were killed after 153 days. All were macro- as well as micro-scopically *quite normal.*

The first animal, fed on *fresh cabbage,* was killed after 105 days as a control for the first of the 110 deg. animals. It showed some œdema, but was otherwise macro- as well as micro-scopically quite normal. The second guinea-pig was killed after 153 days; this animal did not show any macro- or micro-scopical alteration. The third animal is still living; that is, after 290 days. Its weight was recently 690 grams; to-day it is 565 grams.

These results represent a new proof of the correctness of the hypothesis mentioned in the article on polyneuritis in poultry: that *also nutriments that are strongly heated may be of importance as regards the etiology of scurvy.*

5. *On Etiological Analogies between Scurvy in Guinea-pigs and Human Scurvy.*

It remains for us to examine whether *human* scurvy can be caused by food similar to that which we have mentioned in the foregoing experiments.

There exist at present three theories on the etiology of human scurvy. The *first one* supposes the disease to be of an *infectious nature.* As far as we have been able to see, this theory, however, is only based on speculation.

The *second theory* supposes scurvy to be due to *damaged food.* We are of the opinion that neither has this theory been supported by any convincing observations. In fact, the theory is based on experiences made during famines, campaigns, sieges, or on board ships on long voyages; that is, under circumstances where it must be admitted that various articles of food are often damaged. On such occasions, however, the *selection* of nutriments also will be very limited; that is, the diet will become one-sided: the more because people usually do not like to eat damaged food, or eat little of it, and prefer to keep to the other, that is, mostly *farinaceous* food.

The *third theory* supposes the disease to be caused by a *one-sided diet*—especially a food which does not contain, or contains too little of, fresh aliments. It seems to us that the facts by which Lind, Hirsch, and so many other writers, have supported this theory are in every respect convincing; they agree also with our own experiments.

Of these facts we may draw attention to some observations showing that scurvy has repeatedly taken its rise where the food consisted of the same, or about the same, nutriments which we have used in our experiments on guinea-pigs.

To commence with the *infantile scurvy*: Barlow has pointed out that this disease seems often due to the injurious effect of farinaceous food. As regards older individuals, there exist several observations showing that scurvy has taken its rise where bread or other grains were used for months without any addition. Such cases are, for instance, quoted by the Danish author, Adolph Meyer, as well as by Evans. Cases of this kind were also observed under the so-called thirst-cures of Schroth, which were the fashion in Germany in the middle of the nineteenth century ("Semmel-Kur"). Again, we may recall the interesting observations of Dr. Curran, during the epidemic of scurvy which broke out after the failure of the potato-crop in Ireland, 1846-7. Four-fifths of his numerous patients had only lived on bread and coffee, or tea. (The food of the remaining one-fifth had consisted of grains of various kinds, in some cases with some meat or fish, but without any green vegetables or potatoes.)

We may further mention that Dr. Wessel, in Finmarken, Norway, has been kind enough to communicate to us that he has observed several cases of exactly the same kind. These patients had lived for three to four months on bread or groats, in some cases also on a soup of rye-flour. Some of them had also a few times got an addition of a little meat or fish, but without any fresh vegetables or potatoes.

Finally, Delpech and Bucquoi saw, during the siege of Paris, 1870-71, several individual cases where the patients developed scurvy, having lived for three to four months exclusively on bread or rice, or on bread *and* rice, with or without three to four meals of meat or vegetables.

It is true, in most cases of scurvy, the food has consisted of more varied kinds of aliments. But there exist several reports on epidemics after a food which differed very little from that mentioned above. For instance, Maitland has pointed out in the *Lancet*, of 1900 (vol. ii, p. 1164), that Sepoys regularly get scurvy within from two to three months when eating only rice and dhal. But as soon as they obtain, in addition to this food, fresh potatoes or lemons, they recover after a short time. We may further draw attention to the epidemic of scurvy that broke out, in 1846, in the prison Akerstius, in Christiania. Owing to the failure of the potato-crops, potatoes were not distributed from the middle of the year; from this time, also, the prisoners only exceptionally got any fresh milk, and the food was reduced to bread, porridge of barley-groats and barley-flour, some broth, some ale, and a soup made of ale. In addition, they got once a week, butter, and once a week 6 ozs. of meat and 2 ozs. of pork. Some months afterwards the epidemic broke out, and did not cease until fresh potatoes were, in 1847, again introduced into the diet. Finally, it is worth mentioning that several prisons were, during the siege of Paris, 1870-71, visited by the malady; the food consisted of rice, bread, dried peas and beans, some wine and coffee, with sugar; in part the beans and peas were replaced by macaroni and barley-groats, boiled with a little fat. (Delpech, Lasèque, and Legroux).

Concluding Remarks.

We have seen that a one-sided diet consisting of grains, groats, and bread regularly produces in guinea-pigs a disease that is, macro- as well as micro-scopically, quite consistent with scurvy.

On the other hand, we have found that this disease does

not appear when the animals are fed only on fresh cabbage or boiled fresh potatoes. Again, it is produced by an exclusive feeding on *dried* potatoes. That is, in accordance with human scurvy, this disease, too, is only produced by some but not by all aliments.

We have further found that the disease is influenced favourably by the nutriments which are known in human pathology as "*anti-scorbutica*"; but that *cabbage* loses some but not all of its anti-scorbutic power when boiled for half an hour at 110 deg. Cent.

Finally, we have quoted examples showing that the same or similar nutriments that produce the disease in guinea-pigs have also at times produced scurvy in *man*.

On the other hand, we have not hitherto been able to produce the malady that has been the proper object of our researches; we have not been able to produce the younger brother of scurvy—that is, ship beri-beri. It is true, we have repeatedly seen appear, after an addition of anti-scorbutic nutriments to grains or bread, a disease with œdema, but without hæmorrhages. But the œdema did not occur regularly; nor was it accompanied by neuritis. We are, therefore, at present not able to form any distinct idea on the proper causes of ship beri-beri. The same applies to the question as to the precise causes of the influence of grains, and so on.

Discussion.

Sir Thomas Barlow said the paper just read contained a summary of the most exhaustive, complete, and detailed investigation hitherto made on the subject of scurvy. It was specially interesting to note that the anatomical results obtained by our *confrères* in guinea-pigs were similar to those observed in the human subject. The parallelism was more marked between guinea-pigs and infants than between guinea-pigs and adults, for obvious reasons. In the former case there was a more striking parallelism both as regarded hæmorrhages under the periosteum and in the bones themselves, and further as regarded fractures and fragilities. As to prophylaxis, it was very important that it should be definitely ascertained whether heating milk up to a certain temperature was safe, and what that temperature was. Dilution, moreover, has some influence, for in France, where they do pasteurise, but where they do not dilute, milk, scurvy rickets is less common than in England.

SIR ALMROTH WRIGHT, while expressing high appreciation of the valuable facts set forth in the paper, lamented the absence of theories. In his opinion, scurvy was due to excess of acids—the alkalinity of the blood was appreciably diminished, and lactate of soda was needed to restore the balance. He thought lactate of soda should be used in the early stages, when alkalinity of the blood was demonstrably lowered, without waiting for subperiosteal hæmorrhages, tenderness to touch, and the like. He deplored the fact that such large quantities of lime juice all over the world were being vainly used, in the absence of correct ideas concerning the theory of the production of the disease.

SIR PATRICK MANSON was also fond of theories. He held the relationship between scurvy and beri-beri to be expressed by the formula that the inappropriate diet which leads to scurvy predisposes to beri-beri; and he further held that variations in the physiological elements of individuals are sufficiently important to determine that in one case the peripheral nerves, in another the cardiac plexus of the pneumogastric, in a third the machinery concerned with absorption in the subcutaneous tissues, shall bear the brunt of attack.

DR. DURHAM remarked that as theories were on the wing, he would refer to the observations of Dr. Garland Hopkins on "tryptophane-free diets." The absence of this particular constituent, which was found in many, but not in all, protein diets, seemed to play an important part in determining the incidence of scurvy. If Sir A. Wright was inclined to doubt the ability of heated foods to cause mischief, he invited him to live for one fortnight exclusively upon any meat in combination with tinned brussels-sprouts.

DR. BUCHANAN pointed out that tinned meats were not necessarily exposed to a temperature of over 100 degrees Centigrade.

MR. GOADBY referred to the fact that guinea-pigs' teeth more closely resemble the teeth of the human infant than those of the human adult; hence, presumably, the parallelism in the effects produced in disease.

DR. DANIELS said that on steamers, ship beri-beri was seen entirely unassociated with scurvy.

DR. PAYNE asked whether beri-beri occurred on outward-bound ships? Did it occur on new ships, and on ships which have not sailed in Eastern waters?

DR. MYER COPLANS, referring to the paper on scurvy which he read before the Society in 1904, pointed out that the overheating of food, in so far as the Eastern Transvaal cases were concerned, could be dismissed. In that instance all the scurvy-stricken natives subsisted on unpeeled maize. As regards the value of lactate of sodium as a cure for infantile scurvy, he was in some doubt; in the Transvaal cases of scurvy, such treatment was without avail. In his view, the differences between sterilised and new milk were vital rather than chemical. He had found that sterilised milk acts as a medium for the unrestrained growth of certain organisms, while new milk possesses marked bacteriacidal activity. None of the facts brought forward were inconsistent with his views as to the infectivity of scurvy and the value of mouth antiseptics, both as a prophylactic and therapeutic measure.

Reply by Professor Axel Holst.

It will not be easy to answer several of the questions that have been laid before us. With respect to the connection of the disease of our guinea-pigs with rickets, we have sometimes seen indications of a proliferation of osteoid substance; but these indications were slight, and, as a rule, absent. With respect to hæmorrhages in orbita, we have found them in one animal; they were connected with exophthalmos. In another animal we found bloody urine. Hæmorrhages in the stomach and in the kidneys were found in several animals.

Sir Almroth Wright has given prominence to the opinion that scurvy is due to an intoxication by the acid salts contained in grains, bread, and so on. Dr. Frölich and I admire this theory. Though we have started our experiments from quite other views, and though we did not, for a long time, know Sir Almroth Wright's papers, we have arrived at the same results as he has predicted, I may say in a quite prophetic way: that is, that grains and flour produce scurvy. However, we are in doubt whether his explanation concerning the acid salts is the right one. I am very fond of theories; we must always form theories; if we do not, we cannot make experiments. But I am still more fond of facts And one fact is this: that dried potatoes produce scurvy in guinea-pigs, though we have found their ashes strongly alkaline. It is true, that before being dried

in the manufactories, they are boiled in water containing some hydrochloric acid; but so far as we have seen, this acid does not suffice to produce any acid reaction of the ashes. I may also add that dogs are probably very little susceptible to an acid intoxication; because these animals are able to neutralise the acids by means of ammonia. However, in spite of this fact, we have seen a dog presenting, in all essentials, the same alterations of the bone-marrow as we have found in our guinea-pigs. This dog had by accident been fed by its owner for several months on a porridge of boiled oaten-flour and on Indian corn. It became weak, and was killed. We did not make the post-mortem, but we obtained several ribs and tubular bones for examination; in all bones we found a very extensive and wholly typical alteration of the bone-marrow.

But notwithstanding these facts, Dr. Frölich and I are not, at present, inclined to draw any definite conclusion concerning the theory of Sir Almroth Wright. With respect to the objections of Sir Patrick Manson, I admit that we have not hitherto been able to produce, in any convincing fashion, cases of ship beri-beri. Apart from the disease of poultry, which disease we consider as scurvy in poultry, we have only twice seen polyneuritis in our guinea-pigs. I am, nevertheless, not quite satisfied that *human* scurvy, or diseases related to the latter, necessarily must be complicated with another malady in order to be connected with neuritis. I do not pretend that I have found many evidences in support of this view. But I have found some. This applies to several scorbutic cases occurring during the Crimean war; the patients did not feel the ground when walking. The same applies to cases suffering from a "taint of scurvy" during the North American war of rebellion; the patients suffered from partial paralysis. Finally, similar cases were observed during the siege of Paris; and I have found publications showing that the physicians of Paris were, during the siege, in doubt whether the epidemic was scurvy or beri-beri or the so-called "acrodynie." Exactly the same doubt was, for a time, emphasised by some physicians during the Crimean war, until the prevalence of pronounced scorbutic cases became manifest.

Under these circumstances I may ask whether ordinary human scurvy, too, may not possibly be connected with neuritis to a larger extent than appears to be the case from the ordinary publications. For instance, in cases of ordinary scurvy, knee-jerks may often be wanting.

However, I confess that we have not been able to produce, in an at all convincing manner, cases of ship beri-beri. I admit also that neuritis seems to be—according to the communications of Sir Patrick Manson, and other of the speakers whom I have heard with so great interest to-night—much more frequent in cases of ship beri-beri than I had imagined, and than appears from the publications of Nocht.

Finally, I may add that possibly there may sometimes occur cases looking like scurvy but which have another etiology. In this connection, the observations of Dr. Coplans are very interesting indeed. In Germany, too, there has been observed an epidemic of a disease presenting appearances very like scurvy, but without any connection with food. This disease broke out in a prison, and was of an infectious nature (Kühn).

OBITUARY.

SURGEON-GENERAL SIR JOSEPH FAYRER, BART., K.C.S.I.

M.D., LL.D., F.R.C.S., F.R.C.P.

Physician-Extraordinary to H.M. the King.

THE incidents of Sir Joseph Fayrer's strenuous and fruitful life have been related fully and frankly by himself, in a volume entitled *Recollections of My Life*, published in 1900. Since his death, which took place at Falmouth on May 21st last, at the age of 82, lengthy notices of his remarkable career, founded mainly on these *Recollections*, have appeared in the papers, medical and lay. It seems, therefore, unnecessary to reproduce in these *Transactions* details which have already been so amply recorded elsewhere. Epidemics and epidemiology have, however, so largely entered into Fayrer's experiences, work, and writings, and his connection with the Epidemiological Society has been so prolonged, so valued, and so useful, that a sketch of his life in relation to this department of medical study cannot fail to be interesting. It is worthy of note that his resolve to devote his life to the profession of medicine was generated by his attention and interest being arrested by a severe epidemic of yellow fever in the island of Bermuda. He was then nineteen years of age. His previous education had been somewhat desultory, and he had studied engineering and spent a year at sea, but neither occupation was congenial or promising. His father was a retired naval officer, and at this time held an appointment connected with the penal establishment at Bermuda. This circumstance gave his son an introduction to the surgeons in charge of the Naval Hospital, which resulted in his serving a sort of apprenticeship therein, learning compounding and dressing, and studying the elements of anatomy. From this time he applied himself with ardour and energy to the profession which constituted his life-work, and commanded his whole heart and power. He studied at Charing Cross Hospital, and was house-surgeon to the Westminster Ophthalmic Hospital under the Guthries. He threw himself with characteristic force into his

work, and gained several medals and certificates. In 1847 he became a Member of the Royal College of Surgeons, and served for a few months in the Royal Navy at Haslar. He then resigned his commission temporarily, for the purpose of accompanying Lord Mount-Edgcumbe on a prolonged Continental tour, in the course of which he gained experience of military surgery in the insurrection at Palermo and revolution at Rome, attending on the wounded under fire. This was his first experience of calmly performing the duties of his profession under circumstances involving acute danger to life, repeated afterwards at Rangoon and Lucknow, with increased peril and coolness. He renewed his medical studies at Rome, and obtained the degree of M.D. in February, 1849. He also learnt Italian, and took an interest in art and antiquities, which added zest to many subsequent journeyings. On his return to England he served for a few months in the Artillery at Woolwich. Appointed an assistant-surgeon in the Bengal Medical Service, he arrived in Calcutta on the 9th of October, 1850. On the voyage out he displayed courage and strength, by the firm repression of mutiny among the recruits under his medical charge. After serving at Cherrapunjee and Dacca, he was appointed to the Burma Field Force. At Cherrapunjee he made important observations regarding the phenomenal rainfall of that station, and at Dacca distinguished himself by the sense and independence with which he handled a serious outbreak of cholera in the 7th Bengal Native Infantry. His service in Burma as surgeon to the field hospital, medical storekeeper, and civil surgeon of Rangoon, was so intrepid and valuable that Lord Dalhousie selected him for the coveted appointment of Residency Surgeon at Lucknow, where he remained from 1854 till 1858. The part which he took in the defence of Lucknow is matter of history, and the stirring events of the siege are related with graphic fidelity in his *Recollections*. He gained acute knowledge of the influence of a depressing and damaging environment on the health of the beleaguered garrison. Cholera and small-pox were rife, provisions were scanty and inferior, and scurvy common; and the significant remark is made that "all amputations are proving fatal." Infective disease was, in fact, rampant, under unfavourable conditions and insanitary surroundings. His invaluable work—general and medical—was warmly acknowledged and handsomely rewarded; but he left Lucknow at the close of the siege broken in health and impoverished in circumstances, and

was obliged to take furlough in order to recruit. He settled in Edinburgh, and attended medical classes in the University; obtaining the degree of M.D. by special examination, in March, 1859. He became a Fellow of the Royal and Botanical Societies, and accompanied Professor Balfour on a botanising tour to the Continent. He was also elected F.R.C.S.E. Appointed Professor of Surgery in the Calcutta Medical College, he arrived at Calcutta on the 29th of April, 1859. His first act was to refresh his knowledge of anatomy by a complete dissection of the body. His brilliant carear in Calcutta, which lasted till March, 1872, is well known. He rapidly took a leading position as a medical man, scientist, and citizen, and earned by his professional and public work a very high reputation. His work in the College Hospital is embodied in two interesting volumes, entitled *Clinical Surgery in India* (1866), and *Clinical and Pathological Observations in India* (1875). His results were disappointing, on account of the prevalence of "hospitalism," and his mind was greatly exercised by the phenomena and causes of this form of infective disease, of which he had previously had such painful experience at Lucknow. He described the symptoms and post-mortem appearances observed faithfully, and attributed the causation to insanitary conditions. It remained for Lister to demonstrate the origin and remedy of this class of communicable diseases, and when Lister's methods were subsequently resorted to in Calcutta, "hospitalism" disappeared. An enumeration of the appointments held by Fayrer in Calcutta indicate well his great energy and wide interests: Fellow and President of the Medical Faculty, University of Calcutta; President of the Bengal Branch of the British Medical Association; President of the Asiatic Society; Justice of the Peace for the town of Calcutta. He served for a time as personal surgeon to Lord Mayo, and was selected in 1870 to accompany the Duke of Edinburgh, as medical attendant, throughout his Indian tour. He commenced in 1869 those memorable experiments regarding snake venom, which were embodied in the magnificent work entitled *The Thanatophidia of India*, published in 1871. This was the commencement of a great series of researches, in which the names of Vincent Richards, Weir, Mitchell, Lauder Brunton, Wall, Martin, Fraser, Calmette, Lamb, and Rogers are prominent, furnishing an example of the inspiring and stimulating influence of Fayrer's temperament and example in scientific work. From his position and practice, his thoughts were

necessarily largely claimed by epidemiology and sanitation; and much of the work which he subsequently accomplished in London in these subjects had its foundation laid by his Indian experiences. Unable from failing health to prolong the strain of Calcutta work, he was obliged in 1872 to seek rest in England. After serving as a member of the Medical Board at the India Office, he was appointed in 1874 to succeed Sir James Ranald Martin as President, with the rank of Surgeon-General. He resigned the Indian Medical Service in consequence, and for twenty-one years he filled that onerous and responsible office. He was elected a Fellow of the Royal College of Physicians, and practised as a consulting physician. His career in London was full of useful activity in many directions, and he rose to a very high position in the estimation of the profession and the public. His attention was largely devoted to tropical diseases, especially those of an epidemic character, and he kept himself *au courant* with the rapid progress which has been made in our knowledge of the pathology, causation, prevention, and treatment of these diseases during the last quarter of the nineteenth century. He joined the Epidemiological Society in 1875, and was constant in his attendance, and took an active part in its proceedings. In 1879-81 he occupied the Presidential Chair, and delivered two thoughtful and instructive addresses on the "State and Progress of Epidemiological Science." On retiring from the Chair he became a Vice-President, and in 1902 he was elected an Honorary Member of the Society: a distinction which he greatly valued. On the 13th of July, 1900, a commemoration dinner was held to celebrated the jubilee of the foundation of the Society. On this occasion, Sir Joseph Fayrer proposed the "memory of the Founders of the Society," in feeling and graceful terms; and at his suggestion telegrams of greeting were addressed to Sir John Simon and Sir Edward Sieveking, the only survivors of the original founders. Two Papers were contributed by Sir Joseph Fayrer to the *Transactions* of the Society: one in 1879, on the "Relation of *Filaria Sanguinis Hominis* to the Endemic Diseases of India." The discoveries of Lewis, Manson, Bancroft, and others had recently opened out a new field of pathology, in which the pathogenetic function of animal parasites and the agency of blood-sucking insects in harbouring, developing, and transmitting these were established on a basis of demonstration. Fayrer marshalled the data clearly and exhaustively; and though in the light of present knowledge mistakes and omissions are evident,

still the communication served a great purpose in taking stock of the ascertained facts, arousing interest and discussion, and indicating the lines of future research. The other Paper, read in February, 1882, was on "Malaria." At this time a great revolution was taking place in regard to the pathology and etiology of infective endemic and epidemic diseases. Dynamical and chemical theories were yielding to vital and parasitic doctrines, and forces and miasms being supplanted by pathogenetic organisms. Hansen's discovery of the bacillus lepræ in 1874, and Koch's demonstration of the tubercle bacillus in 1881, had paved the way for further disclosures of similar kind. Laveran's immortal detection of the plasmodium malariæ in the erythrocytes in 1880 had aroused attention, but as yet hardly commanded belief; and the work of Manson, Ross, Golgi, Bignami, Grassi, and others was still wanting to place the parasitical causation of malarial disease on a basis of certainty. Fayrer's attitude was one of suspense and doubt. While citing the doctrines of Lancisi, and dwelling on tropical, climatic, and seasonal influences, he saw that forces and miasms were not competent to explain all the phenomena of malarious disease, and indicated the need of a *tertium quid* to account for anomalies. He was not prepared to accept the bacillus of Klebs and Crudeli, nor the plasmodium of Laveran; but counselled further inquiry and patience. The same spirit of conservatism is manifested in the able article on "The Climate and Some of the Fevers of India," which he contributed to the second volume of Allbutt's *System of Medicine* (1897). It is very remarkable how largely epidemiology and tropical diseases—mostly endemic and epidemic—entered into his London work and writings. In 1881 he delivered the Lettsomian Lectures, and took for his subject dysentery and diarrhœa; and in 1882 the Croonian Lectures on the Fevers of India. He wrote on cholera, sunstroke, beri-beri, dengue, bronchocele, elephantiasis, liver abscess, and many other subjects, and always held in view the practical and preventive aspects. His mind and disposition were throughout dominated by the main purpose of his profession—the relief of suffering, the prevention and cure of disease, and the prolongation of life. He represented India at the International Sanitary Conferences at Amsterdam and Rome in 1883 and 1885, and was President of the Section of Practical Medicine at the Congress of Hygiene and Demography in London in 1891. He was also a pioneer in sanitary assurance, and acted as President of the Sanitary Assurance Society. He

drew attention to the value of the baet fruit in dysentery, and of a pure milk diet in tropical diarrhœa. He also wrote on the *Health of European Children in Bengal*, and *The Preservation of Health in India*. These are some indications of the strength and extent of his efforts to throw light on tropical pathology, and ameliorate health in warm climates. He was an active member of the Army Sanitary Commission, and devoted himself to improving the sanitary surroundings of the soldier. In 1875 he was selected to accompany the Prince of Wales (now King Edward VII) as medical adviser during his memorable tour in India. It was a very responsible charge, and his duties were fulfilled with characteristic judgment and independence. His advice, grounded on carefully-considered information, and intended to avoid unnecessary risks, was not always acceptable at the time, but was eventually acknowledged as sound and wise.

Of the many distinctions and decorations which he received from Universities, Governments, and Societies, attesting the respect and esteem in which he was held as a man and physician, it is unnecessary to present a catalogue in this place. Suffice it that they were numerous and well-merited. Nor was his life devoted entirely to science and medicine. He was a good sportsman, an accomplished linguist, a great reader, and devoted to art. He retained his fondness for the sea to the last, and found Falmouth not only a good health resort, but an ideal harbour for yachting and fishing.

Fayrer was one of Nature's noblemen. He rose to eminence in whatever pursuit he followed, and to high position in whatever society he moved; this he did, not through self-seeking or pushing, but by virtue of his fine character, lofty aims, and well-directed industry. He was a loyal friend, and ever true to the interests of his profession and service. He strove to exalt both. He was a kindly doctor, and a most hospitable and generous man. After the trials and losses of Lucknow he contributed the *batta* and prize-money which he received at the close of the siege to the Medical Benevolent College at Epsom, of which he was a Governor. He was elected as a Consulting Physician to Charing Cross Hospital and the Italian Hospital, and served as a Governor of Charing Cross and Guy's Hospitals, Wellington College, and the Gordon Boys' Home. He was also a most interested and useful member of the senate of the Army Medical School at Netley, and seldom failed to be present at the prize givings at the conclusion of the

Session, when it was his habit to address a few kindly words of encouragement to the newly-commissioned officers.

The foregoing sketch, which might have been greatly elaborated, presents the picture of a man of amiable disposition, strong moral power, good intellectual capacity, and great and sustained industry, always directed to the promotion of the welfare of mankind. From first to last, he was actuated and guided by generous and worthy aims, and he spared neither time nor effort in the endeavour to attain them.

K. M

THE

EPIDEMIOLOGICAL SOCIETY OF LONDON.

THIS Society, which was founded in 1850, resolved in 1907 to become the Epidemiological Section of the amalgamation of Medical Societies now known as THE ROYAL SOCIETY OF MEDICINE, which was founded in that year. Henceforth the meetings of the Epidemiological Section will be held at the rooms of the Royal Society of Medicine (20, Hanover Square, W.), at 8.30 P.M., on the Third Friday of every month, with the exception of June, July, August September, and December.

Particulars as regards Fellowship of the Royal Society of Medicine, or Membership of its Sections, can be obtained from the Secretary of the Society at 20, Hanover Square. The annual subscription for Fellows is £3 3*s.*, that of Members of Sections £1 1*s.*

The present volume (vol. xxvi) of the *Transactions of the Epidemiological Society of London* is therefore the last which will be published, and it may interest the members both of the Epidemiological Society and of the Epidemiological Section of the Royal Society of Medicine to know that back volumes of the *Transactions*, as also the Index Volume (1855 to 1900), can still be obtained from the publishers, Messrs. Williams and Norgate, 14, Henrietta Street, Covent Garden, W.C.

Epidemiologists anxious to secure back numbers of the *Transactions* will do well to apply to the publishers at an early date, as certain of the volumes are already out of print, and of others there are but few copies remaining. (See overleaf.)

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